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THE AMERICAN REVIEW OF TUBERCULOSIS

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MEDICAL SECTION OF NATIONAL TUBERCULOSIS ASSOCIATION

CONTENTS

Tuberculosis Attack and Death Rates of Household Associates. The Influence of Age, Sex, Race, and Relationship. RUTH R. PUFFER, L. D. ZEIDBERG, ANN DILLON, R. S. GASS, AND R. H. HUTCHESON 111

Disseminated Nodular Pulmonary Infiltrations of an Indeterminate Nature in Apparently Healthy Persons. AARON D. CHAVES AND HANS ABELES 128

Diffuse Pulmonary Granulomatosis in Young Women Following Exposure to Beryllium Compounds in the Manufacture of Radio Tubes. Further Observations and Report of Nine Additional Cases. PAUL SLAVIN 142

Simultaneous Pulmonary Resection and Thoracoplasty in the Treatment of Pulmonary Tuberculosis. F. HENRY ELLIS, JR., O. THERON CLAGETT, AND DAVID T. CARR 159

The Prognosis of Tuberculous Meningitis. ROBERT DEBRÉ 168

Growth Pattern and Virulence of Tubercle Bacilli. DIRAN YEGIAN AND JOSEPH KURUNG 181

Use of Oxidation-Reduction Dyes in the Determination of Virulence of *Mycobacteria in Vitro*. F. JEAN WILSON, CATHERINE KALISH, AND CHARLES H. FISH 187

A Comparative Study of the Hemagglutination Test for Antibodies and Its Hemolytic Modification in Tuberculosis. MOLLIE MOLLOY AND THADDEUS J. KOTT 194

Effects of Simultaneous Skin Tests on Size of Tuberculin Reactions. CRETYL CRUMB, PAUL MEIER, AND FLORENCE B. SEIBERT 201

Case Reports:

Transthoracic Removal of Calcified Lymph Node Causing Hemoptysis by Bronchial Erosion. HERBERT C. MAIER 206

A Rare Complication of Tuberculous Mesenteric Lymphadenitis. A Case of Fatal Hemorrhage from Abdominal Aorta into Jejunum Through a Tuberculous Lymph Node. RACHEL S. SANDROCK, GEORGE L. EMERSON, AND MARION S. EMERSON 210

Correspondence: Tuberculomas of the Mediastinum. LOUIS SCHNEIDER AND CLIFFORD F. STOREY; Hyaluronidase Effect on BCG Vaccination. E. F. JAMES AND SVEN BERGQVIST 215

American Trudeau Society: Notes 219

Abstracts 21

ANNUAL MEETING—BOSTON, MASS.
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See inside back cover

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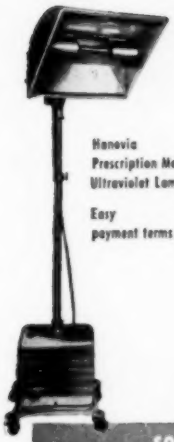

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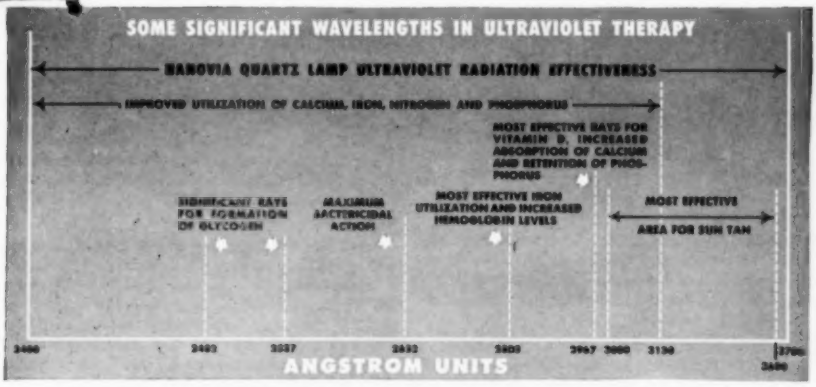
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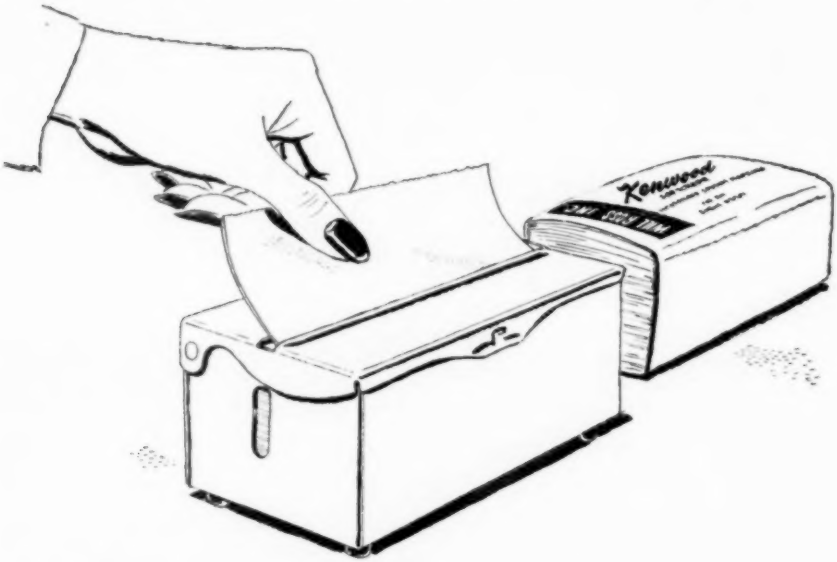

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VOLUME 65 *February 1952* NUMBER 2

TUBERCULOSIS ATTACK AND DEATH RATES OF HOUSEHOLD ASSOCIATES[1,2]

The Influence of Age, Sex, Race, and Relationship

RUTH R. PUFFER, L. D. ZEIDBERG, ANN DILLON, R. S. GASS, AND R. H. HUTCHESON

(Received for publication September 26, 1951)

Introduction

For further knowledge regarding the reasons for the development of clinical tuberculosis in an individual person, multiple factors need to be considered in a population under close observation over a long period of time. The effect of exposure to "sputum-positive" cases (1, 2, 3) on the household associates of those cases is well known. Also, previous analyses (4, 5) have indicated that persons closely related genetically to a person with tuberculosis have high attack and death rates from tuberculosis. However, analyses considering both household exposure to "sputum-positive" disease and relationship to the members of the household are needed in order that both factors may be judged correctly. Animal studies (6), twin research (7), and epidemiologic studies (5) have indicated that the genetic factor, as well as exposure to tubercle bacilli, is deserving of evaluation. Such studies are needed for administration of a sound control program and to guide research directed toward prevention of the development of clinical tuberculosis in the individual.

Plan of Study

Composition of groups: In the Williamson County Tuberculosis Study, household associates of persons with tuberculosis (termed index cases[3]) have been placed under observation and followed closely by examinations in the clinic and by visits of public health nurses. Since the Study was established in December, 1931, 767 households have been investigated and followed because of a diagnosed case of tuberculosis. In the early years of the Study until 1941, households of newly diagnosed cases of tuberculosis, both active and inactive, were followed;

[1] From the Tennessee Department of Public Health, Nashville, Tennessee.

[2] This investigation was made possible by the financial support of the Division of Medicine and Public Health of the Rockefeller Foundation.

[3] In order to simplify the subsequent discussion, the inanimate term "case" is used hereinafter for the designation of these persons.

while in the later years, only households of index cases with active manifest tuberculosis have been taken up for investigation and close observation. Of these 767 households, 298 (38.9 per cent) had a "sputum-positive" or fatal index case. In this group of index cases, several persons died from tuberculosis without tubercle bacilli being demonstrated in the sputum. These deaths were included in the group of "sputum-positive" index cases because the experience of the household associates with respect to the prevalence of tuberculous infection and disease and the incidence of disease was similar to that of the associates of index cases proved to be "sputum-positive".

The analyses reported in this paper will be limited to the experience of the household associates of these 298 "sputum-positive" index cases, hereafter referred to as the "sputum-positive" group. During the period of observation, 60 new cases of tuberculosis, 152 deaths from all causes, and 37 deaths from tuberculosis have occurred in these household associates. The factors, age, sex, race, and relationship will be evaluated in the persons who have been exposed to "sputum-positive" cases[4] of tuberculosis.

The experience during observation of 1,358 household associates of "sputum-positive" index cases has been analyzed and will be presented. The period of observation began with the investigation of the household and has continued to the present, except when all household members died or moved from the county. Data have been analyzed for the 200 white households through April 1950 and for the 98 Negro households through April 1951.

Method of analysis: The method of analysis is the same as that developed by Frost (8) and used in previous publications (4, 5, 9). Tuberculosis attack rates are obtained by dividing the number of new cases which developed during the period of observation by the person-years of observation and multiplying the quotient by the unit 1,000. A person-year is one person followed for one year and is used to replace population in the denominator, since account has to be taken of the period of observation as well as the number of persons under observation. A new case of tuberculosis is a manifest case (in accordance with the classification of Opie) in whom signs or symptoms of the disease are present in addition to roentgenographic evidence of a tuberculous lesion. A few cases of manifest childhood tuberculosis are included in which there were clinical and roentgenographic findings according to Opie's criteria. In the calculation of death rates, person-years replace population in the denominator.

This is an experience of persons who have been heavily exposed to tubercle bacilli, since all members of these households have been in close association with a "sputum-positive" case. In fact, it has been shown that three-fourths of the children less than 15 years of age reacted positively to tuberculin, with nearly as high a percentage for those less than 5 years of age (10). Since the percentages of white and of Negro children found to be tuberculin reactors were high and similar (77.1 white and 74.2 Negro), this can be considered as a group of persons

[4] The experience in the household is limited to those who were present in the household at the same time as the "sputum-positive" index case. Those who entered after the death of the index case are excluded.

in which a very high proportion has already been infected. The fact that the percentages are similar for the two racial groups is noteworthy, since attack rates of clinical disease and death rates differ considerably for the two groups, as will be revealed in this paper.

Results of Analyses

TUBERCULOSIS ATTACK RATES

Tuberculosis attack rates in the two racial groups will be presented first, with consideration of age, sex, and relationship to the index case. The 1,358 household associates were followed for 8,754 person-years or each one was followed, on the average, for 6.4 years[5]. Sixty new cases of clinical tuberculosis developed during observation and the over-all attack rate was 6.9 per 1,000 person-years.

TABLE 1

NUMBER OF NEW CASES OF TUBERCULOSIS DURING OBSERVATION WITH ATTACK RATES PER 1,000 PERSON-YEARS OF HOUSEHOLD ASSOCIATES OF WHITE "SPUTUM-POSITIVE" INDEX CASES* BY AGE AND SEX

AGE GROUP IN YEARS	TOTAL			MALE			FEMALE		
	Person-Years	New Cases	Rate per 1,000	Person-Years	New Cases	Rate per 1,000	Person-Years	New Cases	Rate per 1,000
Total	5,487.75	30	5.5	2,807.00	15	5.3	2,680.75	15	5.6
Under 5	236.25	3	12.7	138.25	3	21.7	98.00	0	—
5–14	1,045.50	0	—	583.50	0	—	462.00	0	—
15–24	1,152.75	11	9.5	657.00	5	7.6	495.75	6	12.1
25–34	699.00	8	11.4	329.00	2	6.1	370.00	6	16.2
35–54	1,235.50	3	2.4	587.25	2	3.4	648.25	1	1.5
55+	1,118.75	5	4.5	512.00	3	5.9	606.75	2	3.3

* Cases of tuberculosis.

Attack Rates According to Age and Sex

The experience of the 879 household associates of 200 white index cases is given in table 1 by age and sex. The tuberculosis attack rates by age and sex are shown in figure 1.

The attack rates by age groups reveal that there are certain ages when the persons who have been exposed to tubercle bacilli are at the greatest risk of developing tuberculosis. The attack rate was high in early childhood (less than 5 years of age). Although children 5 through 14 years of age were known to have been infected with tubercle bacilli in a high proportion, they did not develop clinical tuberculosis in that age group. The tuberculosis attack rate was zero

[5] Each person is followed and included in this experience for the period that he remains in the household. This limits the period of observation, since children usually leave the household on marriage, on induction into the armed services, or for positions out of the county, and so forth. One hundred and sixty-two of the associates entered these households during observation. Many of these were children who were born into the household.

for the 5- through 14-year age group. In young adult life the attack rates were high, 9.5 per 1,000 person-years for those 15 through 24 years and 11.4 per 1,000 for those 25 through 34 years of age. In later adult life, however, the attack rates were low, 2.4 per 1,000 for associates 35 through 54 years, and 4.5 per 1,000 for those 55 years and older.

These attack rates indicate that the periods of life when white persons who had household exposure to tubercle bacilli were at greatest risk of developing clinical disease were infancy and early childhood (less than 5 years) and young adult life (15 through 34 years of age). The age factor seems to be more important than the time of exposure to tubercle bacilli. For example, there were 1,045.50 person-years of experience in the age group 5 through 14 years without a single new case. However, of these same persons who had experience also in the 15- through 34-year age group, 5 new cases developed in their 705.25 years of ex-

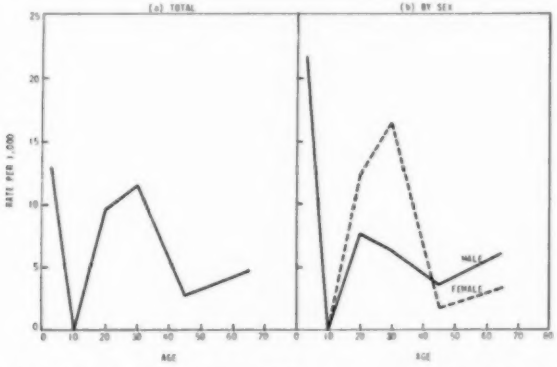

FIG. 1. Tuberculosis attack rates per 1,000 person-years during observation of white household associates of "sputum-positive" index cases (cases of tuberculosis), by age, (a) total and (b) by sex.

perience, and the attack rate was 7.1 per 1,000 person-years. These 5 children had reacted to tuberculin at the time of investigation; so, although they were already infected, they failed to develop clinical disease until they were in the age group 15 through 34 years.

These findings by age are similar to the results of the analysis by Downes (11) for Cattaraugus County, New York. In her study, the attack rates were higher than in the present one, but were high in the same age groups, namely, less than 5 years, 15 through 19 years, and 20 through 29 years of age.

The data for Williamson County were sufficiently large at this time to be analyzed according to sex. The young females 15 through 24 years and 25 through 34 years of age experienced exceedingly high attack rates. For males, the attack rates were high in young adult life, but cases continued to occur in older age groups. These results verify the clinical impression and indicate the

great risk for young females with household exposure to a "sputum-positive" case of tuberculosis.

The experience of household associates of Negro index cases is similar in some respects to that of associates of white index cases but major differences are

TABLE 2

NUMBER OF NEW CASES OF TUBERCULOSIS DURING OBSERVATION, WITH ATTACK RATES PER 1,000 PERSON-YEARS OF HOUSEHOLD ASSOCIATES OF NEGRO "SPUTUM-POSITIVE" INDEX CASES* BY AGE AND SEX

AGE GROUP IN YEARS	TOTAL			MALE			FEMALE		
	Person-Years	New Cases	Rate per 1,000	Person-Years	New Cases	Rate per 1,000	Person-Years	New Cases	Rate per 1,000
Total	3,266.25	30	9.2	1,622.75	12	7.4	1,643.50	18	11.0
Under 5	118.75	1	8.4	53.25	1	18.8	65.50	0	—
5–9	341.75	2	5.9	156.00	1	6.4	185.75	1	5.4
10–14	453.00	8	17.7	219.50	1	4.6	233.50	7	30.0
15–24	746.25	8	10.7	426.00	4	9.4	320.25	4	12.5
25–34	432.75	1	2.3	223.50	0	—	209.25	1	4.8
35–54	641.25	5	7.8	302.50	2	6.6	338.75	3	8.9
55+	532.50	5	9.4	242.00	3	12.4	290.50	2	6.9

* Cases of tuberculosis.

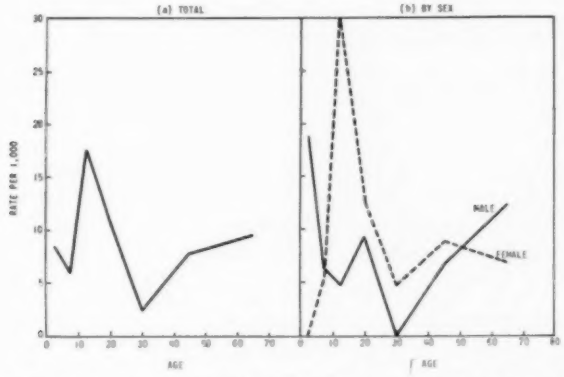

FIG. 2. Tuberculosis attack rates per 1,000 person-years during observation of Negro household associates of "sputum-positive" index cases (cases of tuberculosis), by age, (a) total and (b) by sex.

noted. Thirty new cases developed during the period of observation of the associates of Negro index cases. The attack rates by age and sex are given in table 2 and are shown in figure 2.

The tuberculosis attack rate of 9.2 per 1,000 person-years for these Negro associates was nearly twice the attack rate of 5.5 per 1,000 person-years for the

white associates. Thus, although the prevalence of infection was the same for the two racial groups, the incidence of clinical tuberculosis was greater for the Negro.

The pattern of tuberculosis attack rates by age for these Negro household associates has several noteworthy features. First, children 5 through 14 years of age did not have a zero attack rate as did the white children. Even in children 5 through 9 years of age, 2 new cases developed. In the 10- through 14-year age group, a very high attack rate of 17.7 per 1,000 person-years was noted. Four of the 8 new cases in this age group occurred in 14-year-old children. The attack rate for these Negro associates was also high for those 15 through 24 years of age. Thus, the age period of greatest risk for the Negro household associates was 10 through 24 years of age while for the white associates it was slightly later, 15 through 34 years of age. Since Negro children are known to mature at an earlier age than do white children, these high attack rates at an earlier age are not surprising.

Figure 2 also shows that in the Negro household associates, as in the white associates, the young females were particularly selected for attack.

When the experience during observation was analyzed as of January 1, 1941 (4), the attack rates of both white and Negro household associates of "sputum-positive" index cases were higher than those obtained in this analysis. For the first ten years of the Study, the attack rates were found to be 7.6 for the white and 20.5 per 1,000 person-years for the Negro associates; whereas, after twenty years of observation, the attack rates were 5.5 and 9.2 per 1,000 person-years, respectively. The extension of the experience for another ten years has resulted in the accumulation of few new cases in certain age groups, such as adults 35 years of age and older, although it has increased the person-years of observation. Moreover, Negro households investigated in recent years have not had as many new cases develop as those investigated in the earlier years of the Study. A similar reduction in the attack rate in Negro families has been reported by Downes (12). For a group of 97 Negro families in Harlem she obtained an attack rate of 23.2 per 1,000 for the years 1938 to 1941 and a rate of 9.1 per 1,000 person-years for the years 1942 to 1947.

Attack Rates According to Relationship

The experience of household associates has been divided into two groups according to genetic relationship to the index case. The first group consists of close relatives, that is, the parents, siblings, and children of index cases. The second group includes all other household members, such as nieces and nephews, grandchildren, and so forth, consorts, and those with no genetic relationship, such as sons-in-law, daughters-in-law, and so forth. In table 3 is shown the composition of these two groups with the number of persons in each and also the number of person-years of experience.

Close relatives of index cases had more than half of the person-years of experience of both white and Negro household associates. However, since 45.1 per cent of the white experience and 38.5 per cent of the Negro was for other members of the households, the significance of close relationship to the index

TABLE 3

NUMBER AND PERSON-YEARS OF OBSERVATION OF HOUSEHOLD ASSOCIATES OF "SPUTUM-POSITIVE" INDEX CASES,* ACCORDING TO RELATIONSHIP AND RACE

RELATIONSHIP	WHITE			NEGRO		
	Number	Person-Years		Number	Person-Years	
		Number	Per cent		Number	Per cent
Total	879	5,487.75	100.0	479	3,266.25	100.0
Close relatives	471	3,014.75	54.9	303	2,007.25	61.5
Children	306	2,009.25	36.6	135	840.50	25.7
Siblings	93	506.00	9.2	102	599.25	18.3
Parents	72	499.50	9.1	66	567.50	17.4
Other members	408	2,473.00	45.1	176	1,259.00	38.5
Other relatives	132	795.75	14.5	72	588.00	18.0
Consorts	123	869.75	15.8	41	283.25	8.7
No relation	153	807.50	14.7	63	387.75	11.9

* Cases of tuberculosis.

TABLE 4

NUMBER OF NEW CASES OF TUBERCULOSIS DURING OBSERVATION, WITH ATTACK RATES PER 1,000 PERSON-YEARS OF HOUSEHOLD ASSOCIATES OF WHITE "SPUTUM-POSITIVE" INDEX CASES* BY RELATIONSHIP, AGE AND SEX

AGE GROUP IN YEARS	TOTAL			MALE			FEMALE		
	Person-Years	New Cases	Rate per 1,000	Person-Years	New Cases	Rate per 1,000	Person-Years	New Cases	Rate per 1,000
Close Relatives									
Total	3,014.75	22	7.3	1,623.25	11	6.8	1,391.50	11	7.9
Under 15	764.00	3	3.9	460.50	3	6.5	303.50	0	—
15-34	1,234.25	16	13.0	707.75	6	8.5	526.50	10	19.0
35+	1,016.50	3	3.0	455.00	2	4.4	561.50	1	1.8
Other Members									
Total	2,473.00	8	3.2	1,183.75	4	3.4	1,289.25	4	3.1
Under 15	517.75	0	—	261.25	0	—	256.50	0	—
15-34	617.50	3	4.9	278.25	1	3.6	339.25	2	5.9
35+	1,337.75	5	3.7	644.25	3	4.7	693.50	2	2.9

* Cases of tuberculosis.

case can be studied in this group of persons exposed to "sputum-positive" tuberculosis. The experience of the white household associates is presented in table 4 and the attack rates are shown in figure 3.

Of the 30 new cases of tuberculosis in white household associates, 22 were close relatives and 8 were other members of these households. Since the numbers are

small, the attack rates are calculated for only three age groups: less than 15 years, 15 to 34 years, and 35 years and older. For those less than 35 years of age the attack rates appeared to be somewhat higher for the close relatives than for other members of households. Considering these rates by sex, the young female relatives were noted to have high rates. Since the experience is small, the significance of results depends on consistency of the pattern of attack and death rates in both racial groups.

Similar data for Negro household associates are presented in table 5 and figure 4. Although the differences according to relationship are not as great as in the white associates and are not large enough to be termed significant, they suggest that genetic relationship may be a factor deserving further consideration and evaluation in Negroes. Greater susceptibility of the Negro race as a whole to tuberculosis may tend to overshadow the factor of relationship. The attack rate for the young female close relatives was very high, due to high rates in the 10-

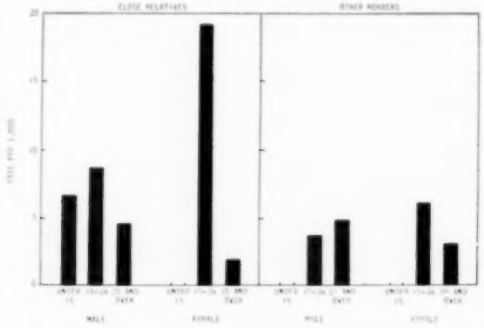

FIG. 3. Tuberculosis attack rates per 1,000 person-years during observation of white household associates of "sputum-positive" index cases (cases of tuberculosis), according to relationship, sex, and age group.

through 14-year age group of children of index cases. This was also observed for the female close relatives in the white household associates. Eight of the 9 new Negro cases in close relatives less than 15 years of age were children of index cases. The 2 new cases in the other members were nephews of index cases.

MORTALITY OF HOUSEHOLD ASSOCIATES DURING OBSERVATION

Death rates from all causes and from tuberculosis, as well as tuberculosis attack rates, are useful in evaluating the significance of factors concerned in the epidemiology of tuberculosis. While the accurate recording of the date of onset of clinical tuberculosis is especially difficult, deaths are definite events which are well recorded[6]. The assigned cause of death may be erroneous, however,

[6] Within the households under observation, deaths are known because of close observation. In Tennessee, however, death registration is known to be incomplete, especially in sparsely populated areas.

particularly when tuberculosis progresses so rapidly to death that it is confused with pneumonia or influenza, and so reported. The effect of such errors on material of the Study can be minimized by comparing the death rates from all

TABLE 5

NUMBER OF NEW CASES OF TUBERCULOSIS DURING OBSERVATION, WITH ATTACK RATES PER 1,000 PERSON-YEARS OF HOUSEHOLD ASSOCIATES OF NEGRO "SPUTUM-POSITIVE" INDEX CASES* ACCORDING TO RELATIONSHIP, AGE, AND SEX

AGE GROUP IN YEARS	TOTAL			MALE			FEMALE		
	Person-Years	New Cases	Rate per 1,000	Person-Years	New Cases	Rate per 1,000	Person-Years	New Cases	Rate per 1,000
Close Relatives									
Total	2,007.25	21	10.5	1,021.75	8	7.8	985.50	13	13.2
Under 15	556.25	9	16.2	274.00	1	3.6	282.25	8	28.3
15–34	730.00	7	9.6	439.00	4	9.1	291.00	3	10.3
35+	721.00	5	6.9	308.75	3	9.7	412.25	2	4.9
Other Members									
Total	1,259.00	9	7.1	601.00	4	6.7	658.00	5	7.6
Under 15	357.25	2	5.6	154.75	2	12.9	202.50	0	—
15–34	449.00	2	4.5	210.50	0	—	238.50	2	8.4
35+	452.75	5	11.0	235.75	2	8.5	217.00	3	13.8

* Cases of tuberculosis.

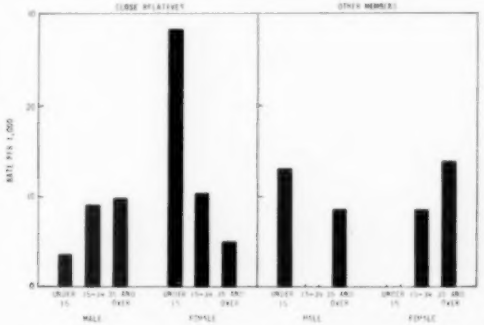

FIG. 4. Tuberculosis attack rates per 1,000 person-years during observation of Negro household associates of "sputum-positive" index cases (cases of tuberculosis), according to relationship, sex, and age group.

causes among household associates with those in the general population. In this way, the effect of household exposure to "sputum-positive" cases and of other factors can be studied.

Death Rates by Age

The death rates from all causes are presented first. In table 6 are shown the number of deaths and the death rates per 1,000 person-years for white and Negro associates of "sputum-positive" index cases by age group. For use in evaluating the mortality in these associates, the average annual death rates for Tennessee for the mid-period of the experience, 1940 to 1942, are given also in column 4 (white) and column 9 (Negro) of the table. These average rates in the general population of Tennessee were applied to the person-years of experience for each age group and the expected number of deaths obtained. The death rates in the white population in column 4 were applied to the person-years in column 1 and the expected deaths for each age group obtained for column 5. Likewise,

TABLE 6

NUMBER OF DEATHS DURING OBSERVATION, WITH DEATH RATES PER 1,000 PERSON-YEARS OF HOUSEHOLD ASSOCIATES OF "SPUTUM-POSITIVE" INDEX CASES* AND AVERAGE DEATH RATES FOR TENNESSEE FOR 1940–1942 BY AGE AND RACE

AGE GROUP IN YEARS	WHITE					NEGRO				
	Person-Years (1)	Deaths		Tennessee Average Rate (4)	Expected Deaths (5)	Person-Years (6)	Deaths		Tennessee Average Rate (9)	Expected Deaths (10)
		Number (2)	Rate (3)				Number (7)	Rate (8)		
Total	5,487.75	77	14.0	8.8	64.1	3,266.25	75	23.0	14.7	49.4
Under 5	236.25	5	21.2	13.3	3.1	118.75	6	50.5	19.2	2.3
5–14	1,045.50	5	4.8	0.9	0.9	794.75	4	5.0	1.6	1.3
15–24	1,152.75	7	6.1	1.9	2.2	746.25	11	14.7	5.7	4.3
25–34	699.00	6	8.6	2.7	1.9	432.75	6	13.9	8.5	3.7
35–44	596.75	5	8.4	4.5	2.7	306.00	4	13.1	12.9	3.9
45–54	638.75	6	9.4	8.6	5.5	335.25	8	23.9	23.7	7.9
55–64	587.25	6	10.2	17.9	10.5	267.00	14	52.4	36.9	9.9
65–74	347.50	14	40.3	42.1	14.6	197.50	14	70.9	47.5	9.4
75+	184.00	23	125.0	123.3	22.7	68.00	8	117.6	98.0	6.7

* Cases of tuberculosis.

the Negro death rates in column 9 were multiplied by the person-years in column 6 to give the expected deaths in column 10. The numbers of expected deaths for each age group were added to obtain the total number of deaths expected in these household associates if they had experienced at each age the mortality rates in Tennessee for 1940 to 1942. The number of deaths expected in the white associates (column 5) may then be compared with the number observed (column 2). Similarly, the number of deaths expected in the Negro associates (column 10) may be compared with the number observed (column 7).

In the experience of white associates, 77 deaths have occurred while 64.1 were expected. In the Negro associates, 75 deaths were observed while 49.4 were expected. The ratio of observed to expected deaths of 1.5 for the Negro associates was higher than the ratio for the white associates of 1.2.

For comparison of mortality by age, figure 5 shows the death rates by age of white and Negro associates and death rates in the general population of Tennessee for the two groups. The death rates of the household associates were higher in both racial groups in infancy and young adult life than in the general population. These are the periods of life when the risk of developing tuberculosis is great.

In order to judge the excessive mortality, the observed deaths may be compared with the deaths from tuberculosis which would be expected in these house-

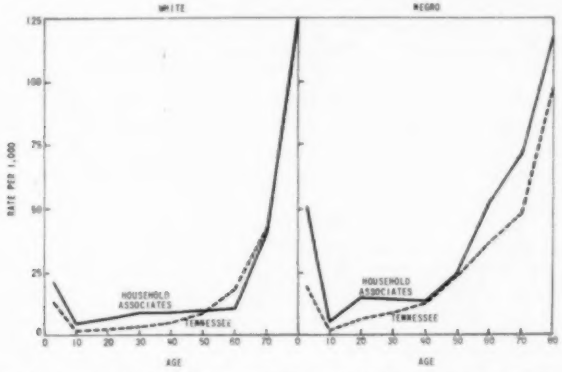

FIG. 5. Death rates per 1,000 person-years of household associates of "sputum-positive" index cases (cases of tuberculosis) and average death rates for Tennessee, 1940–1942, by age and race.

TABLE 7

NUMBER OF OBSERVED AND EXPECTED DEATHS FROM ALL CAUSES AND FROM TUBERCULOSIS OF WHITE AND NEGRO HOUSEHOLD ASSOCIATES OF "SPUTUM-POSITIVE" INDEX CASES*

RACE	DEATHS FROM ALL CAUSES			DEATHS FROM TUBERCULOSIS		
	Observed	Expected	Ratio†	Observed	Expected	Ratio†
White	77	64.1	1.2	12	3.8	3.2
Negro	75	49.4	1.5	25	4.8	5.2

* Cases of tuberculosis.

† Observed divided by expected.

hold associates if they had experienced the rates in Tennessee for the general population (table 7). Although reporting of deaths in household associates is complete, it is recognized that registration of deaths in Tennessee is not. However, this deficiency in registration is probably not sufficient to account for the differences observed here. While 12 deaths from tuberculosis were observed in the white associates, 4 were expected. Likewise, there was an excess in the observed deaths in the Negro associates (25 observed and 5 expected). Although a large part of the unusually high mortality from all causes can be accounted for by the excessive number of tuberculosis deaths, that is not sufficient to explain

all of the deaths. For example, in the white, there was an excess of 13 deaths, of which 8 may be attributed to tuberculosis. In the Negro, the excess was 26, of which 20 may be attributed to the mortality from tuberculosis. Thus, it is evident that these household associates of "sputum-positive" cases experienced an unusually high risk of dying from tuberculosis or from other causes.

Death Rates According to Relationship

Mortality from all causes has been studied for the two groups: (*1*) close relatives and (*2*) other members of these "sputum-positive" households. Since the age distributions of the two groups differed from each other and from the population of Tennessee, the death rates for four age groups by sex were applied to the population of Tennessee by race for the mid-year (1941) and age-adjusted death rates obtained. These adjusted death rates are shown in table 8.

In the white associates, the adjusted death rate from all causes for close relatives was 12.4 per 1,000 and, for other members, 10.6 per 1,000; while for the white population of Tennessee the death rate from all causes was 8.8 per 1,000

TABLE 8

AGE-ADJUSTED DEATH RATES PER 1,000 AND TUBERCULOSIS DEATH RATES PER 100,000 PERSON-YEARS OF HOUSEHOLD ASSOCIATES OF "SPUTUM-POSITIVE" INDEX CASES,* ACCORDING TO RELATIONSHIP AND FOR TENNESSEE, 1940–1942, BY RACE

GROUP	DEATH RATE FROM ALL CAUSES PER 1,000		TUBERCULOSIS DEATH RATE PER 100,000	
	White	Negro	White	Negro
Close relatives	12.4	23.9	308.9	934.4
Other members	10.6	18.0	81.8	409.5
Tennessee	8.8	14.7	58.4	152.2

* Cases of tuberculosis.

population. In the Negro population even greater differences were noted, with the adjusted death rate 23.9 per 1,000 for close relatives, 18.0 per 1,000 for other members, and 14.7 for the Negro population of Tennessee. Thus, death rates in both groups of associates exceed the rates in the general population of Tennessee, principally as a consequence of exposure to "sputum-positive" tuberculosis. Of the associates, however, those related genetically to the persons with tuberculosis experienced much higher death rates than did the other members of these households. As in the study of tuberculosis attack rates, the genetic factor as well as the exposure factor evidently is important.

For further study of mortality, the tuberculosis death rates in these households have been analyzed according to age as well as relationship. The experience for the close relatives and for other members of the household is presented in table 9. The tuberculosis death rates for three age groups of close relatives and of other members of white and Negro households are shown in figure 6.

Of the 12 deaths from tuberculosis which occurred among white household associates during the period of observation, 10 were of close relatives of index

TABLE 9

NUMBER OF TUBERCULOSIS DEATHS DURING OBSERVATION WITH DEATH RATES PER 100,000 PERSON-YEARS OF HOUSEHOLD ASSOCIATES OF "SPUTUM-POSITIVE" INDEX CASES,* ACCORDING TO RELATIONSHIP, AGE GROUP, AND RACE

AGE GROUP IN YEARS	CLOSE RELATIVES			OTHER MEMBERS		
	Person-Years	Tuberculosis Deaths		Person-Years	Tuberculosis Deaths	
		Number	Rate per 100,000		Number	Rate per 100,000
White						
Total	3,014.75	10	331.7	2,473.00	2	80.9
Adjusted			308.9			81.8
Under 15	764.00	2	261.8	517.75	0	—
15-34	1,234.25	4	324.1	617.50	1	161.9
35+	1,016.50	4	393.5	1,337.75	1	74.8
Negro						
Total	2,007.25	20	996.4	1,259.00	5	397.1
Adjusted			934.4			409.5
Under 15	556.25	6	1,078.7	357.25	1	279.9
15-34	730.00	9	1,232.9	449.00	1	222.7
35+	721.00	5	693.5	452.75	3	662.6

* Cases of tuberculosis.

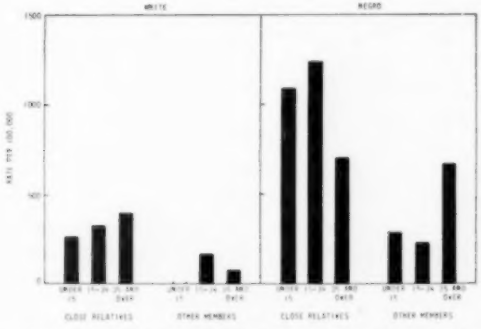

FIG. 6. Tuberculosis death rates per 100,000 person-years of household associates of "sputum-positive" index cases (cases of tuberculosis) for close relatives and other members, by age group and race.

cases and 2 were of other household members. The age-adjusted death rate for the close relatives of 308.9 per 100,000 was approximately four times the rate for other members of these households. In the Negro household associates, 20 of the tuberculosis deaths were of close relatives and 5 were of other members. The

tuberculosis death rate for the close relatives in Negro households of 934.4 per 100,000 was extremely high and more than twice the rate for other members of these Negro households.

The differences in tuberculosis death rates for close relatives and for other members in the three age groups, less than 15 years, 15 through 34 years, and 35 years of age and older, are shown in figure 6. In comparing tuberculosis attack and death rates in close relatives and other household associates (figures 3, 4, and 6), similarity of the pattern of selection is apparent. However, the mortality data show even more emphatically the importance of relationship as an epidemiologic factor responsible for the development of tuberculosis.

The tuberculosis death rates adjusted to the age distribution of the population of Tennessee for the close relatives and other members of the household are shown in table 8. The tuberculosis death rates in the general population are given also for comparison with those in household associates of "sputum-positive" cases. The close relatives experienced tuberculosis death rates five to six times those in the general population of Tennessee. The rates for other members were also higher, with the rate for white members 40 per cent above, and the rate for Negroes more than two and one-half times that for the general population.

The tuberculosis death rates can be used in considering the relative importance of exposure to tubercle bacilli and genetic relationship in the development of a particular case of tuberculosis. Household exposure to "sputum-positive" disease was primarily responsible for the high death rates. However, within this group, those related genetically to the index case were the ones experiencing exceedingly high death rates. Thus, the genetic factor has significance also. Persons related genetically to persons with tuberculosis evidently are more susceptible to the disease than others. When both exposure and genetic relationship are operating, death rates from tuberculosis become exceedingly high.

Comment

The results presented in this paper have practical application in the tuberculosis control program and also are valuable for research. In the control program, emphasis needs to be placed, as in the past, on household associates of "sputum-positive" cases. However, within this group, the white females 15 through 34 years of age and the Negro females 10 through 24 years of age should have frequent examination and close observation. Persons closely related genetically to persons with tuberculosis should be followed and examined, with special attention to those in the critical age group when the risk of developing the disease is greatest. Since age is such an important factor, children of "sputum-positive" cases should be observed frequently in young adult life. As tuberculosis declines in the general population, the emphasis may logically be changed from widespread mass examination to those at greatest risk of attack and death from the disease.

The importance of this approach has been appreciated in New South Wales

Health Department since 1934, for Joyce (13) stated "From 5 to 15 years there are very few cases but a steep rise occurs from 15 to 25 years. There is a second breakdown period from 35 to 45 years. We do not know why these age groups are more susceptible than others but the whole plan of control is based on these known facts." Also their research revealed that genetic relatives should be followed and now their work "extends beyond the patient's home to all members of the family wherever they may be."

In addition to frequent examinations to detect the disease, research is needed to understand why certain persons, especially the young females, are at such great risk of developing tuberculosis and why those related genetically are more susceptible under exposure than those who are not so related to persons with tuberculosis. How do they differ physiologically? Animal research is being carried on by Lurie (14, 15, 16) at Henry Phipps Institute to study susceptibility and resistance to tuberculosis. Similar research extended to the human population is needed to explain why tuberculosis develops in persons of certain age, sex, and relationship. Such research may reveal how resistance in the susceptible person may be developed.

Summary

Tuberculosis attack and death rates have been obtained for the 1,358 household associates of 298 "sputum-positive" index cases (cases of tuberculosis) during the period of close observation in the Williamson County Tuberculosis Study.

The tuberculosis attack rates for the Negro associates were higher than for the white associates. A variation was noted by age group. The highest attack rates were observed in white females in young adult life, 15 through 34 years of age, and in Negro females at a slightly earlier period from 10 through 24 years of age.

The number of deaths from all causes of these household associates was greater than expected, based on the death rates in Tennessee. Seventy-seven deaths were observed in the white associates while 64 were expected; 75 deaths were observed in the Negro associates while 49 were expected.

The attack and death rates for the close relatives (parents, siblings, and children) were found to be higher than the rates for other members of the households. The tuberculosis death rates for the close relatives (308.9 for the white and 934.4 per 100,000 person-years for the Negro) were much higher than the rates for other household members (81.8 for the white and 409.5 per 100,000 person-years for the Negro) and the latter rates were higher than those in the general population of Tennessee (58.4 for the white and 152.2 per 100,000 population for the Negro).

The evidence presented here indicates that age, sex, race, and genetic relationship determine the development of tuberculosis in persons exposed to "sputum-positive" index cases. These factors should be considered in the development of a tuberculosis control program and also in guidance of research. The genetic factor, as well as exposure to tubercle bacilli, is responsible for high attack and death rates.

Sumario

Los Coeficientes de Ataque y Mortalidad por Tuberculosis en los Convivientes: El Influjo de la Edad, Sexo, Raza y Parentesco

Obtuviéronse los coeficientes de ataque y mortalidad por tuberculosis para los 1,358 convivientes de 228 casos con esputo positivo durante un período de observación detenida en un estudio de la tuberculosis en el Condado Williamson.

Los coeficientes de ataque tuberculoso fueron mayores para los convivientes negros que para los blancos. Notáronse variaciones conforme al grupo etario. Los coeficientes más altos correspondieron a las blancas en el período adulto joven, 15 a 34 años inclusive de edad, y en las negras a una época un poco más temprana, de los 10 a 24 años de edad.

El número de muertes por todas causas en dichos convivientes fué mayor de lo esperado, a base de los coeficientes de mortalidad en el Estado de Tennessee. En los blancos hubo 77 muertes cuando sólo esperaban 64; en los negros hubo 75, cuando se esperaban 49.

Los coeficientes de ataque y mortalidad para los parientes cercanos (padres, hermanos e hijos) resultaron ser mayores que para otros de la casa. La mortalidad tuberculosa para los parientes cercanos (308.9 para los blancos y 934.4 por 100,000 personas-años para los negros) fué mucho más alta que para los demás de la casa (81.8 para los blancos y 409.5 por 100,000 personas-años para los negros), siendo estos últimos coeficientes a su vez más altos que los de la población general de Tennessee (58.4 por 100,000 habitantes para los blancos y 152.2 para los negros).

Los datos aquí presentados indican que la edad, el sexo, la raza y el parentesco sanguíneo determinan la producción de tuberculosis en los individuos expuestos a casos con esputo positivo. Hay que considerar, pues, esos factores en la elaboración de un plan de lucha antituberculosa y también en la orientación de las investigaciones. El factor genético así como la exposición a los bacilos tuberculosos participa en los altos índices de ataque y de mortalidad.

Resume

Infection tuberculeuse et taux de mortalité chez les membres d'un même foyer: Influence de l'âge, du sexe, de la race et du degré de parenté

Au cours d'une période de stricte surveillance dans l'enquête du comté de Williamson, le nombre de cas d'infection tuberculeuse et le taux de mortalité pour un groupe de 1.358 individus ont été déterminés. Ces individus appartenaient à des foyers où 208 cas classés comme tuberculeux avec crachats positifs étaient présents.

Le taux des cas d'infection tuberculeuse pour les nègres est plus élevé que pour les blancs. On observe une différence selon le groupe d'âge. Les taux les plus élevés sont observés chez les jeunes femmes de race blanche, de 15 à 34 ans, et légèrement plus tôt, de 10 à 24 ans, chez les femmes de race noire.

Le nombre des décès dus à des causes diverses pour les membres de ces foyers était plus élevé que celui correspondant aux prévisions fondées sur le taux de mortalité dans l'état de Tennessee. Il a été observé 77 décès chez les individus de race blanche alors que les précomptions statistiques indiquent 64; 75 décès ont été observés chez les individus de race noire alors que les présomptions statistiques indiquent 49. Le taux d'infection tuberculeuse et le taux de mortalité pour les parents proches (parents, enfents d'un même père ou d'une même mère, et autres enfants) ont été trouvés plus élevés que les taux correspondants chez les autres membres du foyer. Le taux de mortalité tuberculeuse pour la proche parenté (308,9 pour la race blanche et 934,4 pour 100.000 homme/années pour la race noire) était beaucoup plus élevé que le taux correspondant pour les autres membres du foyer (81,8 pour la race blanche et 409,5 pour 100.000 homme/années pour la race noire). Ces derniers taux étaient plus élevés que ceux se rapportant à la population générale du Tennessee (58,3, pour la race blanche et 153,2 pour 100.000 habitants pour la race noire).

Les données fournies par ce rapport indiquent que l'âge, le sexe, la race et le lien de parenté par le sang jouent un rôle déterminant dans le développement de la tuberculose chez les individus en contact avec des cas classés comme ayant des crachats positifs. Ces facteurs doivent être pris en considération dans l'élaboration des programmes de lutte contre la tuberculose et comme guides dans la recherche. Le facteur génétique, de même que l'exposition au bacille tuberculeux, est responsable du nombre de cas de contamination tuberculeuse et du taux de mortalité élevés.

Acknowledgment

The writers wish to acknowledge the valuable contribution to this research of Dr. H. C. Stewart, former director of the Williamson County Tuberculosis Study.

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DISSEMINATED NODULAR PULMONARY INFILTRATIONS OF AN INDETERMINATE NATURE IN APPARENTLY HEALTHY PERSONS[1]

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INTRODUCTION

As a result of mass chest roentgenography, a surprising number of cases of disseminated nodular pulmonary infiltrations have been discovered in apparently healthy persons. While the list of etiologic agents which could be responsible for such lesions is large and constantly growing (1, 2), it has been the experience of the writers that the exact nature of many of them remain obscure even after careful investigation. The observations made in a series of such undiagnosed cases form the basis for the present report.

PLAN OF INVESTIGATION

SELECTION OF MATERIAL

A large volume of material available from the 23 chest clinics and the survey units of the Bureau of Tuberculosis was screened for cases which fulfilled the following criteria:

1. Discovery on a survey or routine chest roentgenogram of disseminated nodular infiltrations not associated with obvious intrathoracic lymphadenopathy
2. No knowledge of lymphadenopathy or other organ involvement in the past; no other organ involvement at the time of discovery
3. A period of follow-up observations of at least one year for those patients who showed complete roentgenographic clearing spontaneously, and two years for all others
4. Failure to establish a definite diagnosis accountable for the chest findings.

The criteria for selection were fulfilled in 75 cases. The clinical observations, in 57 instances, were limited to those which could be conducted without interrupting the normal activities of the patients who were, for the most part, asymptomatic and unable to understand the need for medical supervision. In 18 cases, however, investigations were carried out in a hospital. All of the persons had, as a minimum, the following work-up: history, including details as to occupational and geographical background; physical examination; examination of sputum or gastric contents for *M. tuberculosis;* serial chest roentgenograms; and serologic tests for syphilis. In almost all instances, the cutaneous reaction to tuberculin was studied.

DESCRIPTION OF MATERIAL

Age and sex: There were 45 males and 30 females; this difference is a reflection of the large number of draftees included in the base material. The distribution of cases by age is noted in table 1.

[1] From the Bureau of Tuberculosis, New York City Department of Health, 125 Worth Street, New York 13, New York; and the Departments of Medicine and Preventive Medicine of the New York Hospital-Cornell Medical Center.

Race: There were 56 white and 19 Negro patients. The distribution of cases by age, sex, or behavior of the pulmonary lesions was not strikingly different in the two races.

Geographic background: In all but 8 cases, the patient was either a life resident of New York City, with travel limited to the immediate confines of the city, or had been living in this city or its environs for many years prior to the discovery of the pulmonary disease.

Occupational background: Detailed questioning did not indicate any significant dust exposure. In no instance could any definite exposure to beryllium be established. Details concerning other environmental factors or personal habits gave no clues as to the possible cause of the nodular lesions.

Other factors: In no instance was the evidence clear that the pulmonary disease was of an allergic nature. In no instance was more than one case found in a

TABLE 1

DISTRIBUTION BY AGE OF 75 CASES OF DISSEMINATED PULMONARY INFILTRATIONS OF INDETERMINATE NATURE

	TOTAL	AGE AT DISCOVERY IN YEARS			
		15-20	21-30	31-40	Over 40
Number	75	7	42	20	6

TABLE 2

75 CASES OF DISSEMINATED PULMONARY INFILTRATIONS
PERIOD OF OBSERVATION IN YEARS

	TOTAL	1-2	2-3	3-5	5-10	OVER 10
Number	75	14	15	18	16	12

family, and none occurred as part of an epidemic. There was no particular seasonal incidence.

Period of observation: The periods of observation, measured from the time the nodular lesions were first detected to the time of the most recent chest roentgenogram, are listed in table 2. The mean period of observation was three to five years. In two instances the illness was followed to a fatal termination.

OBSERVATIONS

OBSERVATIONS AT TIME OF DISCOVERY

Symptoms and Physical Findings

Forty-four persons were asymptomatic. Twenty-four had mild, mostly transient, respiratory symptoms; among these were 4 recently recovered from an acute febrile illness. Seven had minor complaints not related to the pulmonary disease.

No significant positive findings on physical examination were noted except for persistent localized rales in 6 persons and the presence of a few small peripheral lymph nodes in 7 persons.

Cutaneous reaction to tuberculin: The results of the *tuberculin* reactions are noted in table 3. No correlation existed between reaction and subsequent behavior of the lesions.

Other skin tests done were of insufficient numbers to draw conclusions. A positive *histoplasmin* reaction was present in 2, and a positive *coccidioidin* reaction in one, of 14 persons tested with both antigens. *Blastomycin* skin tests done in 3 persons were negative. A *Kveim* test was done in 10 persons, with a positive reaction in 3 of them.

Laboratory findings: In approximately one-third of the cases in which determinations were made, the leukocyte and erythrocyte counts, the erythrocyte sedimentation rate, and chemical determinations of the blood, including serum proteins, were noncontributory. Four persons had a positive serologic test for syphilis.

Examinations of sputum or gastric contents by stained smear and culture in 54 persons and of stained smear alone in 21 failed to reveal the presence of *M. tuberculosis.*

TABLE 3

75 Cases of Disseminated Pulmonary Infiltrations
Tuberculin Reaction at Time of Discovery

Total Number	Not Tested	.01 mg. OT			1.0 mg. OT			Combined Results		
		Number Tested	Positive	Negative	Number Tested	Positive	Negative	Number Tested	Positive to Either Test	Negative to Both Tests
75	4	71	15	56	56	16	40	71	31	40

Of 4 persons with lymph node biopsies, 2 had findings of "chronic lymphadenitis" and 2 had those of a sarcoid type of granuloma. A lung biopsy done in one instance revealed a foreign-body type of granuloma. One tonsillar biopsy was not helpful.

Roentgenographic Findings

Thirty-one persons had normal chest films obtained from one month to seven years (mean, two and one-half years) prior to discovery. In 2 instances, roentgenograms taken one year prior to discovery of manifest disease revealed a few faint nodules in the upper lung fields which had been overlooked.

The roentgenographic findings at the time of discovery showed considerable variation, but were arbitrarily classified in accordance with the *predominating* characteristics of the lesions (table 4) under the following descriptive terms:

Fine nodular infiltrations: Very small, usually discrete, nodules giving a stippled or ground-glass appearance, frequently in association with reticulation

Medium-sized nodular infiltrations: Nodules larger than fine and up to 3 mm. in diameter, usually soft and irregular in appearance

Large nodular infiltration: Most nodules were 3 to 5 mm. in diameter, usually soft and irregular in appearance.

Mixed: Nodular infiltrations of any size in association with predominantly linear types of density, either of the reticular variety or, more frequently, those which seemed to follow the bronchovascular markings.

Both lungs were symmetrically involved in 72 cases. In 36, the lesions were distributed uniformly from apex to base; in 13, they were more numerous in the upper lung fields; in 16, they were concentrated in the mid-lung fields; in 7, the lower lung fields were favored. Predominantly unilateral involvement was noted in 3 persons.[2] Confluence of the nodules was a frequent occurrence, particularly in the peripheral zones.

Roentgenographic studies of the hands, obtained in 71 cases, were normal.

TABLE 4

75 CASES OF DISSEMINATED PULMONARY INFILTRATIONS

RELATIONSHIP BETWEEN INITIAL AND SERIAL ROENTGENOGRAPHIC FINDINGS

SERIAL FINDINGS	TOTAL	INITIAL CHARACTERISTICS			
		Fine Nodules	Medium-Sized Nodules	Large Nodules	Mixed (Predominantly Linear)
Total	75	10	23	10	32
Regression	56	6	22	8	20
Complete	40	3	18	8	11
Incomplete	16	3	4	0	9
Stationary	13	3	1	2	7
Progression	6	1	0	0	5

FOLLOW-UP OBSERVATIONS

Serial Roentgenographic Findings

No correlation existed between the extent of involvement and the ultimate behavior of the lesions. None of the persons developed intrathoracic lymphadenopathy or disseminated calcification.

The relationship between the initial roentgenographic characteristics and serial findings is noted in table 4.

Regression: In 56 patients, the lesions showed spontaneous clearing which was *complete* in 40 (no residual abnormalities) and *incomplete* in 16 (residual nodular and linear densities). The approximate duration of clearing, measured from the time of discovery to the time of complete disappearance or stabilization, is noted in table 5. In 43, regression was continuous, usually gradual, but occasionally occurring with remarkable and unpredictable rapidity. In 12, progression of the disease for a two- to forty-eight-month period preceded the clearing. In one case, considerable fluctuation during the course of two pregnancies was noted over a

[2] These persons all had persistently negative cutaneous reactions to tuberculin.

two and one-half year period. In no case was a recurrence noted once the lesions disappeared completely.

Stationary lesions: In 13 cases, there was no evidence of change for three to thirteen, or an average of six, years.

Progression: In 6 patients, at the end of at least four years of observation, a greater degree of pulmonary involvement remained than was present initially. Two patients showed a gradual increase in nodular lesions, with some tendency towards confluence. One, in whom early regression had occurred, eventually showed considerable increase in nodulation, with concomitant development of pulmonary fibrosis and an enlarged heart. In 3 patients a remarkable evolution was seen from nodular to linear densities, with the simultaneous appearance of multiple emphysematous bullae.

Clinical Course

Sixty-nine persons were afebrile and essentially asymptomatic throughout the period of observation. Repeated physical examinations and laboratory tests continued to be unrevealing.

TABLE 5

75 Cases of Disseminated Pulmonary Infiltrations
Observed Duration of Clearing in 56 Cases with Regression

Type of Regression	Total	Duration of Clearing in Months								
		1-3	4-6	7-12	13-24	25-36	37-48	49-60	Over 60	Not Known
Total	56	3	10	14	11	8	2	2	3	3
Complete*	40	3	10	12	9	4	0	0	1	1
Incomplete†	16	0	0	2	2	4	2	2	2	2

* Mean duration of clearing: 7 to 12 months.
† Mean duration of clearing: 25 to 36 months.

Six persons developed varying degrees of pulmonary insufficiency. One, with considerable residual reticulation after clearing, and a second, with stationary lesions, developed progressive dyspnea on exertion, evidence of cor pulmonale, and secondary polycythemia over a period of ten and thirteen years, respectively. A third, with roentgenographic evidence of progression, died of right heart failure four and one-half years after the pulmonary lesions were discovered. Of the 3 remaining persons, all with extensive pulmonary fibrosis and multiple bullae, one has had slowly progressive dyspnea, cough, and cyanosis over a ten-year period, one has shown remarkable improvement after a critical illness (Case 8), and one died seven years after discovery. Necropsy findings in the latter revealed "multiple air cysts" throughout both lungs and cor pulmonale.

The great majority of the cases received no treatment. Where employed, therapy, including streptomycin in 3 cases and cortisone in one, had no noticeable effect on the course of the disease.

ILLUSTRATIVE CASES

Fine Nodular Infiltrations

Case 1. Fine generalized nodulation with almost complete clearing within ten months.

G. F. was a 27-year-old white male whose survey roentgenogram on May 27, 1949 revealed fine, granular nodulation throughout both lungs (figure 1, left). The tuberculin reaction was negative to 1 mg. of Old Tuberculin. A chest film taken in February 1949, following a four-week bout of "pneumonia," showed similar findings. The patient continued to work while under supervision, complaining only of occasional exertional dyspnea early in the disease. By November 9, 1950 the nodular lesions had shown remarkable clearing (figure 1, right). On August 6, 1951, the patient had no complaints and his roentgenogram revealed no change.

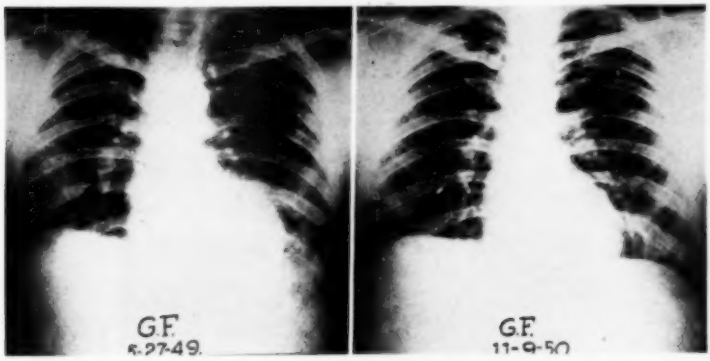

FIG. 1. Case 1 (G. F.) (Left) Widely disseminated fine nodulation with many areas of confluence. (Right) Roentgenogram taken eighteen months later showed that only faint linear densities remained.

Case 2. Fine nodulation with partial clearing during a period of seventeen months.

A. L. was a 38-year-old Negro male whose survey film on November 20, 1942 revealed widely disseminated fine nodulation, with a ground-glass appearance over the mid-portion of the right lung (figure 2, left). Tuberculin reaction was positive to .01 mg. of OT, but several sputum examinations failed to reveal tubercle bacilli on stained smear and culture. The patient continued to work throughout the period of observation, during which his original symptoms of mild cough and slight exertional dyspnea improved, and physical examinations revealed no abnormalities. Following some progression of the disease noted during the first nine months of observation, serial roentgenograms revealed gradual clearing of the nodules until February 9, 1944. Subsequent examinations, including the most recent one on November 30, 1950, showed the patient to be in good health, with no noticeable changes in the residual roentgenographic findings (figure 2, right).

Case 3. Fine nodulation remaining stationary for ten years.

J. S. was a 16-year-old white male whose survey film taken on Feburary 28, 1941 revealed diffusely disseminated fine nodulation, entirely out of keeping with the patient's lack of symptoms or abnormal physical findings. Detailed questioning concerning the patient's

environment and habits were unrevealing. A tuberculin test was negative to 1.0 mg. of OT. Subsequent films to December 1, 1943 revealed no change (figure 3). He was then lost from supervision until April 28, 1948, when he was admitted to an institution for schizophrenia.

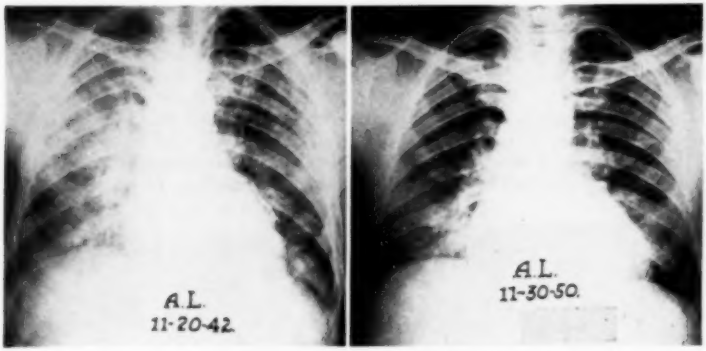

FIG. 2. Case 2 (A. L.) (Left) Fine nodulation, with ground-glass appearance in right midzone. (Right) Roentgenogram taken November 30, 1950 showed residual linear and confluent densities throughout, heaviest at bases.

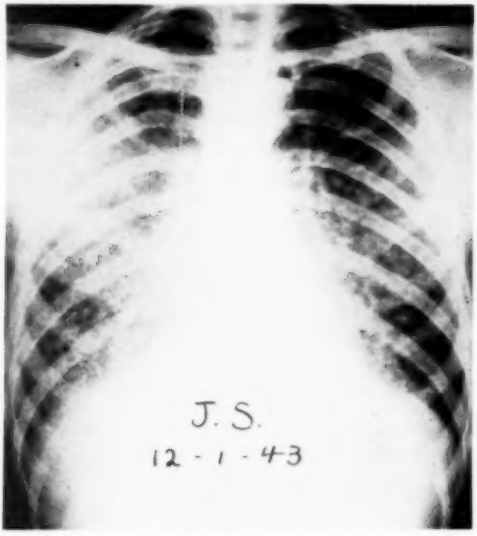

FIG. 3. Case 3 (J. S.) Fine nodulation and reticulation, heaviest at bases

Chest films taken at regular intervals from that time until September 27, 1950 showed no change from the earlier ones. He is reported as being in good physical condition and free of respiratory complaints as of July 9, 1951.

Medium-Sized Nodular Infiltrations

Case 4. Medium-sized nodulation with complete clearing within three months.

A. O. was a 16-year-old Negro girl in whom a survey examination on April 10, 1946 revealed widely disseminated medium-sized discrete nodules, most numerous in the mid-zones (figure 4, left). Her tuberculin reaction to 1 mg. of OT was negative. Even though the patient continued to attend school, the lesions cleared so rapidly that by July 2, 1946 her roentgenogram was normal (figure 4, right). She remained in good health, with normal roentgenograms, until November 9, 1949 when she was lost from supervision.

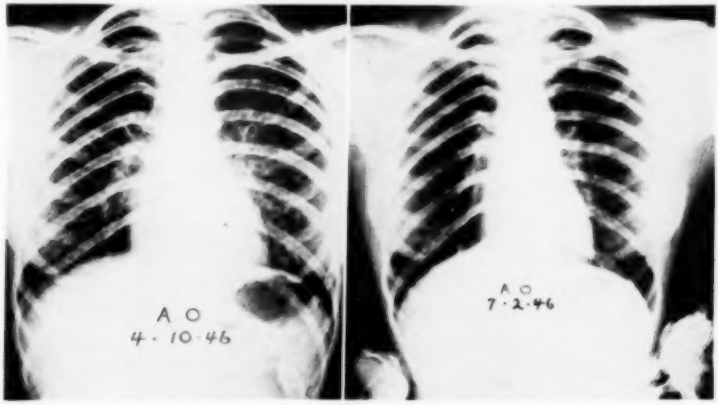

FIG. 4. Case 4 (A. O.) (Left) Discrete medium-sized nodulation. (Right) Normal roentgenogram taken less than three months later.

Large Nodular Infiltrations

Case 5. Large nodulation with complete clearing within one year.

M.S. was a 22-year-old white male whose survey film in July 1947 was normal. A routine chest film taken early in July 1948 revealed widely disseminated, large nodules with some confluence at the periphery (figure 5, left). The patient was admitted to a tuberculosis hospital on July 12, 1948, where he received streptomycin until October 16, 1948, when he left against advice to return immediately to his job as a truck driver. During hospitalization, repeated examinations of sputum and gastric washings failed to reveal the presence of *M. tuberculosis* on smear or culture. A tuberculin test was not done. He ran an afebrile, asymptomatic course, with some roentgenographic improvement by the time he left the hospital. By the summer of 1949 the chest roentgenogram had returned to normal in spite of his arduous physical activities. When seen on January 3, 1950 he was in robust health and had a normal chest film (figure 5, right). Subsequent examination on August 15, 1950 was normal.

Mixed Nodular and Linear Densities

Case 6. Mixed nodular and linear densities with complete clearing within two years.

J. L. was a 27-year-old white male whose survey film on December 26, 1941 revealed a diffuse distribution of small nodular and linear densities, leaving the extreme bases rela-

tively clear (figure 6, left). Tuberculin reaction was negative to 1 mg. of OT. Gradual clearing of the lesions was noted while the patient continued to work until, by January 6, 1944, the chest roentgenogram was within normal limits. Subsequent roentgenographic examinations, including the most recent one on November 2, 1950, were normal (figure 6, right).

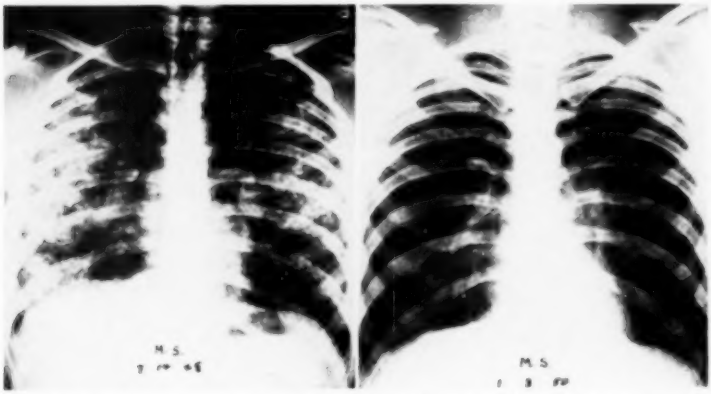

FIG. 5. Case 5 (M. S.) (Left) Large nodulation with considerable coalescence at periphery. (Right) Normal roentgenogram taken seventeen and one-half months later.

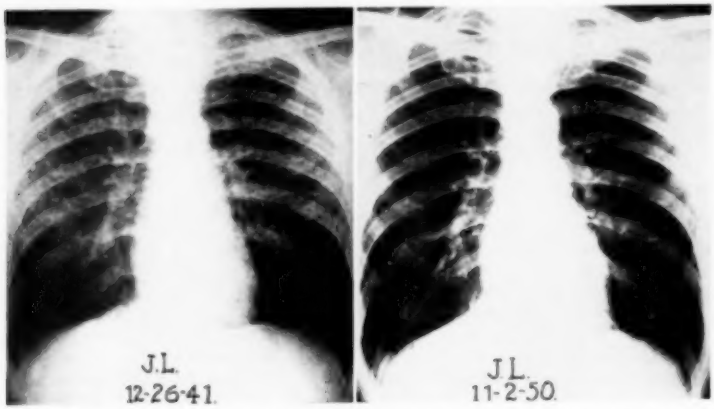

FIG. 6. Case 6 (J. L.) (Left) Mainly linear densities with some nodulation; bases clear. (Right) Normal roentgenogram taken nearly ten years later.

Case 7.[3] Progression of mixed lesions with development of bullae.

E. L. was a 28-year-old white male whose pre-employment films in January and June, 1943, were normal. Another survey film on July 30, 1943 revealed disseminated mixed nodular and linear densities similar to those seen on a film taken August 3, 1943, when the patient first

[3] This case has previously been reported by Rubin (3).

came under Health Department supervision (figure 7A). A tuberculin test was positive to .01 mg. of OT. The patient was hospitalized on January 10, 1944 because of roentgenographic evidence of progression of the disease, although he had remained afebrile and asymptomatic. During the early months of hospitalization, further progression of the mixed lesions was noted (figure 7B). By July, the lesions appeared more linear, and widely distributed areas of bullous emphysema were now evident. In August 1944, the patient developed first a right, and later, bilateral spontaneous pneumothorax which, after a stormy course, slowly

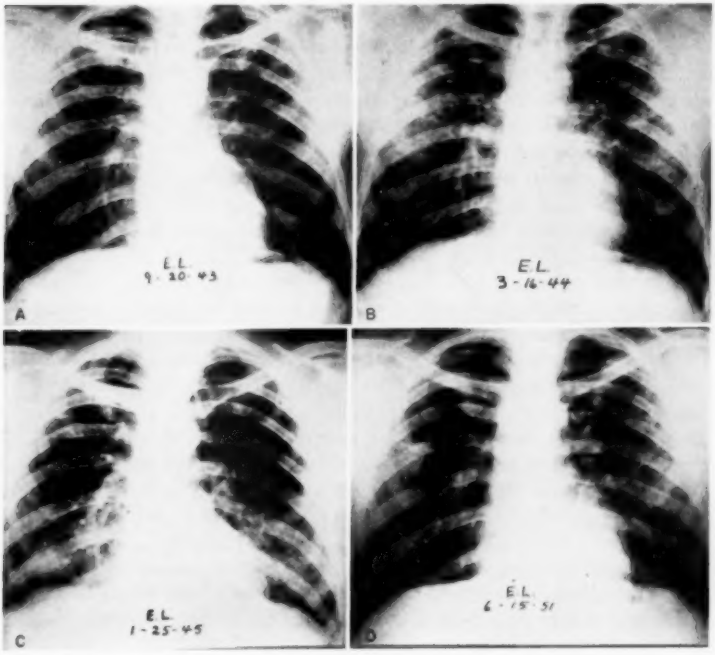

FIG. 7. Case 7 (E. L.) A. Early involvement of upper lung fields with linear and nodular densities. B. Definite progression, with extension into mid-zones (courtesy Montefiore Hospital, Bronx, New York). C. Giant bullae and linear densities, without nodulation (courtesy Montefiore Hospital, Bronx, New York). D. Residual scattered linear densities with confluent patch in right mid-zone. Bullae were evident on fluoroscopy.

responded to treatment, with re-expansion completed in November 1944. Tubercle bacilli were never demonstrated in the cultures and stained smears of the sputum or gastric contents. On discharge from the hospital on January 25, 1945, the roentgenogram revealed multiple bullae, some of giant size, and scattered linear densities (figure 7C). Subsequent films up to April 30, 1946 showed marked decrease in the size and number of bullae with residual linear markings. When last examined on June 15, 1951, the patient was free of complaints and was working for the police force although the chest film at that time revealed interval progression of the pulmonary disease (figure 7D).

Discussion

Although the cases in this study do not conform to the usually accepted criteria of any known clinical entity, the roentgenographic findings closely resemble some of those described in many diseases, the most important of which include: disseminated forms of tuberculosis (4, 5)[4] and the mycoses (6–20)[5]; sarcoidosis (21–30); and pneumoconiosis (3, 31, 32). Long-term clinical and epidemiologic studies of a more intensive kind than were possible with this material are necessary to determine to what extent cases such as those reported here are merely unusual variants of established diseases or actually represent as yet unrecognized conditions. At present, evidence available from several sources where lung biopsies have been done in similar cases merely indicates that most, if not all, of these lesions are granulomatous in nature and are probably caused by a variety of agents not readily identifiable.

Until the time when such lesions can be classified more precisely, the management of disseminated pulmonary nodular densities of an indeterminate nature in apparently healthy individuals must be guided, to a great extent, by a knowledge of what their possible evolution may be. The observations of this study may be helpful in that respect. For instance, in all such cases, while a very intensive investigation to eliminate tuberculosis as a possibility must be carried out, there seems to be little justification for instituting antituberculosis therapy solely on the basis of the roentgenographic findings. Likewise, the pronounced tendency towards spontaneous regression in the majority of these cases would warrant withholding such expensive and potentially hazardous drugs as cortisone or corticotropin (ACTH), in the absence of symptoms or complications, until their application to such cases has been more clearly defined. On the other hand, an awareness that there may be an important relationship between these lesions and the future development of some types of pulmonary fibrosis associated with impaired pulmonary function (33) should encourage prolonged and careful supervision in all similar cases, including those with complete roentgenographic clearing. In particular, it would be well to keep in mind the unpredictable and variable behavior of these lesions in evaluating the results of therapy.

Summary

Accidentally discovered disseminated nodular pulmonary infiltrations of an indeterminate nature were found unassociated with lymphadenopathy or other visceral involvement in 75 apparently healthy persons. Of these, 49 were less than 30 years of age; 56 were white. The mean period of observation was three to five years.

Complete roentgenographic clearing occurred spontaneously within a mean period of seven to twelve months in 40 cases; partial clearing, with evident resid-

[4] During this study the authors encountered five persons who, although otherwise undistinguishable from those included in this series, developed manifest pulmonary tuberculosis more than five years after the accidental discovery of the nodular lesions.

[5] References to certain epidemics (11–18) are included here because of recent studies (19, 20) indicating that they were probably caused by *Histoplasma capsulatum*.

ual fibrosis, occurred during a mean period of twenty-five to thirty-six months in 16; the lesions remained stationary for at least three years in 13. Continued roentgenographic evidence of progression over a period of at least four years was noted in 6 persons, 3 of whom developed multiple emphysematous bullae.

There was no striking correlation between the extent or initial character of involvement on the chest roentgenogram and the ultimate behavior of the lesions. None of the cases developed disseminated pulmonary calcification.

Symptoms of pulmonary insufficiency developed in 6 patients, 2 of whom died. The remaining patients had an asymptomatic course.

The exact nature of these lesions remains obscure, but they probably represent a heterogeneous group of granulomatous conditions—caused by a variety of agents not readily identifiable.

Sumario

Infiltraciones Nodulares Diseminadas de Naturaleza Indeterminada en los Pulmones de Personas Aparentemente Sanas

En 75 personas aparentemente sanas, se descubrieron fortuitamente infiltraciones nodulares diseminadas de naturaleza indeterminada en los pulmones sin asociación con linfadenopatía u otra afección orgánica. De esas personas, 49 tenían menos de treinta años y 56 eran blancas. El período de observación promedió de tres a cinco años.

En 40 casos, hubo espontáneamente completo despeje radiográfico de la lesión en término medio de siete a doce meses; en 16, despeje parcial, con manifiesta fibrosis residual en término medio de veinticinco a treinta y seis meses, en 13, las lesiones permanecieron estacionadas por lo menos tres años, en 6 casos, se notaron continuos signos radiográficos de agravación durante un período mínimo de cuatro años, manifestando 3 de ellos múltiples bulas enfisematosas.

No existía notable correlación entre la extensión o naturaleza inicial de la invasión notada en la radiografía torácica y el comportamiento final de las lesiones. Ninguno de los casos manifestó calcificación pulmonar difusa.

Presentáronse síntomas de insuficiencia pulmonar en 6 casos, 2 de los cuales terminaron en la muerte. Los demás casos mostraron una evolución asintomática.

La naturaleza exacta de dichas lesiones continúa siendo oscura, pero las mismas representan probablemente un grupo heterogéneo de estados granulomatosos, ocasionados por varios agentes que no es fácil identificar.

Resume

Infiltrations nodulaires de nature indéterminée disséminées dans le poumon chez des individus paraissant en bonne santé

Des infiltrations nodulaires de nature indéterminée disséminées dans le poumon, et accidentellement découvertes, ont été trouvées, sans qu'on puisse observer d'adénopathie lymphatique ou de lésions organique associées, chez 75 individus paraissant en bonne santé. Parmi ces sujets 49 étaient âgés de moins de 30 ans, 56 étaient de race blanche. La période moyenne d'observation est de trois à cinq ans.

La disparition complète de l'image radiologique s'est produit spontanément dans une période moyenne de sept à douze mois dans 40 cas; la disparition partielle avec sclérose résiduelle visible s'est produite au cours d'une période moyenne de vingt-cinq à trente-six mois chez 16 sujets; les lésions sont demeurées stationnaires pendant au moins trois ans chez 13 sujets; des signes radiologiques d'évolution continue, pendant une période d'au moins quatre années, ont été observées dans 6 cas, dont 3 ont présenté des bulles emphysémateuses multiples.

Aucune corrélation nette n'existait entre l'étendue ou le caractère initial de la lésion sur les radiogrammes du poumon et les conditions ultimes de l'évolution.

Des symptômes d'insuffisance pulmonaire se sont manifestés dans 6 cas, 2 d'entre eux se sont terminés par la mort. Les autres cas ont eu une évolution asymptomatique.

La nature exacte de ces lésions demeure obscure, elles représentent probablement un groupe hétérogène d'affections granulomateuses causées par des agents variés difficilement identifiables.

Acknowledgment

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DIFFUSE PULMONARY GRANULOMATOSIS IN YOUNG WOMEN FOLLOWING EXPOSURE TO BERYLLIUM COMPOUNDS IN THE MANUFACTURE OF RADIO TUBES

Further Observations and Report of Nine Additional Cases

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INTRODUCTION

Five cases of diffuse pulmonary granulomatosis resulting from exposure to beryllium in the manufacture of radio tubes were reported previously (1). Nine additional cases are presented in this paper. For reference they will be identified in the total series of 14 cases as numbers 6 to 14 inclusive.

Nine patients (Cases 2, 3, 4, 6, 8, 9, 10, 11, and 12) had been working in a factory where beryllium had been used as an ingredient in the coating of filaments, hook wires, and cathodes, and also in the manufacture of automobile headlight lamps.

A detailed description of dust-producing operations leading to atmospheric contamination with beryllium was obtained from 7 patients. No protection was provided against dust inhalation.

The diagnosis of beryllium granulomatosis was substantiated in 5 cases by autopsy findings. Beryllium was recovered from the lungs in each instance.

CASE REPORTS

Case 6. The patient, M. R., was a 22-year-old, unmarried, white woman who was first examined by the writer on November 8, 1949.

The patient had become aware of increasing shortness of breath in the latter half of 1947 during her fourth year of work in a radio tube factory. Later on, she began to lose weight and developed a cough. In June 1949 she was confined to bed for an attack of fever and severe pain in the left chest. She felt very weak, but returned to work on July 19. Within two weeks she became totally disabled. A chest roentgenogram of August 8, 1949 indicated probable pulmonary beryllium granulomatosis.

Occupational exposure: The patient left school at the age of sixteen and obtained employment in a radio tube factory. She worked there steadily for five years and eight months, from January 1944 until August 1949, when she became totally disabled. Her work during the first thirteen months involved no dust exposure. In February 1945 she was transferred to the filament floor and worked there for eighteen months, until August 1946. Her work consisted mainly of handling coated cathodes and filaments. Folding the filaments and inserting them into cathode tubes caused chipping and scattering of the coating. She handled from two to three thousand units a day, and the operation resulted in considerable dust formation. Her place of work was near a drum-cutter, a machine for cutting and nicking coated filaments. The pulverized coating dispersed by the drum-cutter provoked choking and coughing. In August 1946 the patient was transferred to the headlight lamp department. There she was engaged in soldering lamps and in painting mounts with getter paint. Scraping the solder formed considerable dust. The smell of the getter paint caused nausea and coughing.

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Clinical and laboratory studies: Physical examination revealed shortness of breath. The respiration at rest was 32 per minute. The patient was 61½ inches tall and weighed 86 pounds, having lost 14 pounds since the beginning of her illness. Her pulse rate was 76 per minute and the blood pressure was 96 mm. systolic and 64 mm. diastolic. The breath sounds were suppressed over the lower portion of the left chest. Adventitious sounds were present over both lungs. The vital capacity was 1,600 cc.

The chest roentgenogram (figure 1, November 8, 1949) showed a diffuse network of nodular densities overshadowing both lung fields. The horizontal interlobar septum was thickened. The right ventricle was enlarged. The outline of the diaphragm was irregular.

The sputum was negative for tubercle bacilli. The skin tuberculin test was also negative. The urine was negative for beryllium.

Subsequent periodic examinations showed no improvement. Repeated chest roentgenograms revealed no essential changes. The electrocardiogram of September 23, 1950 showed

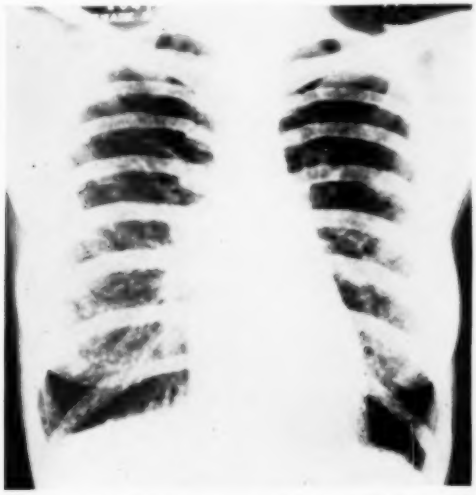

FIG. 1. Case 6. November 8, 1949. Diffuse nodulation. Bulge in pulmonary conus.

a right axis deviation, a P-pulmonale pattern, and an equiphasic QRS-1, indicating a developing cor pulmonale.

The last examination on February 19, 1951 revealed a slight cyanosis. The vital capacity was 1,450 cc., a drop of 150 cc. since November 1949. There was a further weight loss of 1½ pounds. A number of polymorphonuclear leukocytes exhibited toxic granules.

Comment: This patient had been exposed to beryllium for eighteen months while working on coated filaments and cathodes. Her subsequent work for three years in the headlight lamp department apparently also involved exposure to beryllium, the metal having been used in the manufacture of the lamp getters.

Case 7. The patient, M. McG., was a 51-year-old, widowed, white woman who was examined by the writer on February 6, 1950.

The present illness dated from 1937 when she developed a cough and shortness of breath. She also noticed a downward curving of her fingernails. The factory fumes and dust ag-

gravated her cough and she stayed away from work at frequent intervals. In June 1939 she was operated upon for a tumor of the uterus. Her first chest roentgenogram was taken in July 1939. Late in 1939 she returned to work but became permanently disabled in the spring of 1940. For the last ten years her condition remained stationary.

Occupational exposure: The patient left school at the age of fifteen and began to work at sixteen. Until the age of thirty-three she worked in two factories and also as a clerk, waitress, and salesgirl. During that period of employment she was apparently not exposed to dust. In 1931 she started to work in a radio plant and continued there for three years. Her work consisted of cutting wires, baring their ends by stripping off the coating, and then soldering them. The place of work was filled with snowlike dust. In 1934 she changed to a radio tube factory. There her work of inspecting finished tubes involved no dust exposure. In June 1935 she returned to the radio plant where she had worked previously for three years and resumed the job of cutting wires. She quit the factory in the spring of 1940 because of the disabling lung ailment.

FIG. 2. Case 7. March 5, 1947. Diffuse fibrotic changes and nodulation. Calcific deposit in right breast.

Clinical and laboratory studies: The patient appeared to be nervous, and was vague in describing the details of her jobs. Her breathing was accelerated, but there was no apparent respiratory distress at rest. The fingers were clubbed, and the nails were curved downward. Adventitious sounds were heard over both lungs.

Her first available chest roentgenogram of July 8, 1940 showed a diffuse network of nodular densities throughout both lung fields. The horizontal interlobar septum was elevated to the level of the second right anterior intercostal space. A calcific deposit was present near the outer margin of the lower right lung field. The outline of the diaphragm was irregular.

The chest roentgenogram taken seven years later (figure 2, March 5, 1947) showed increased fibrotic changes in both lung fields. The horizontal interlobar septum became further elevated to the level of the first right anterior intercostal space. The upper portion of the mediastinal shadow was widened by enlarged lymph nodes.

Subsequent chest roentgenograms showed no essential changes. The calcific deposit visualized in the right lung field was shown in a left oblique view to be located in the right breast. Roentgenograms of the bones of both hands were negative.

Course: On September 10, 1950, the patient committed suicide by ingestion of "sleeping pills." The day previously, hospitalization for an acute glaucoma of the right eye was advised.

Post-Mortem Examination[2]

Macroscopic examination: The right eyeball was very hard; the right pupil measured 8 mm.; the left pupil, 3 mm.

Dense adhesions were present over the apices of both lungs. The visceral pleura was studded with dark-gray nodules. The upper lobes were retracted and packed with nodules; the other lobes were fairly well aerated; the hilar lymph nodes were enlarged. The muscle of the right ventricle was 3 mm. thick, the muscle of the left ventricle was 1 cm. thick.

Microscopic examination: Only a portion of the right lung was removed for study. Sections showed a widespread fibrosis with typical beryllium nodules. The granulomas contained numerous inclusion bodies.

Spectrographic analysis by two laboratories revealed:

Laboratory 1. Wet lung—130 gm. ..... beryllium—0.4 γ
Laboratory 2. Wet lung—100 gm. ..... beryllium—1.3 γ

Comment: The history obtained from this patient failed to specify the nature of the dust to which she had been exposed for seven years in a radio shop. The difference in the amounts of beryllium recovered from her lung tissue by the two laboratories was apparently due to varying concentrations of the metal in different portions of the lungs. The disease in this case became stabilized without causing enlargement of the right ventricle, and a longer survival period could be expected. The possibility of a granulomatous process in the glaucomatous right eye has not been investigated.

Case 8. The patient, C. L., was a 35-year-old, unmarried, white woman who was first examined by the writer on February 8, 1950.

The patient had begun to complain of shortness of breath and of recurrent headaches in 1943, during her ninth year of work on radio tubes. Her difficulty in breathing grew progressively worse, and she left the factory in September 1948. She obtained employment in a stationery shop, but change of work brought no relief. Her first chest roentgenogram was taken on November 2, 1948. The skin tuberculin test was negative. She was treated for a tired heart and was advised to lessen her activities. After a two weeks' rest she resumed her work in the stationery shop. Four weeks later she became totally disabled. On February 8, 1949, her illness was diagnosed as beryllium granulomatosis. She remained at home. The slightest exertion provoked coughing and aggravated her shortness of breath. Within the last few weeks she noticed intermittent swelling of her ankles. She had had scarlet fever in childhood.

Occupational exposure: The patient began to work in factories at the age of twenty-one. She worked for four and a half years in the mounting department of a radio tube factory. Mounting the micas caused some of the cathode coating to be scraped off in the form of a fine dust. In March 1939 she changed to another radio tube factory, and for the first five years continued as a mounter of top micas. In 1944 she was transferred to the filament floor and for more than three years worked near the spray booths where the cathodes and hook wires were being coated. The air was filled with pulverized coating scattered by the spray guns. From June 1947 until September 1948 she worked as a mounter for experimental work in the engineering department. The place was poorly ventilated. Her last job, in the stationery shop, involved no dust exposure.

Clinical and laboratory studies: The physical examination revealed marked cyanosis. The breathing was shallow and very rapid, ranging between 60 and 65 per minute. The

[2] Performed on September 10, 1950 by Dr. Edward F. Murray.

neck veins were distended. The fingers were clubbed, and the nails were curved downward. The pulse rate was approximately 180 per minute. The second pulmonic sound was markedly accentuated. There were occasional extrasystoles. Adventitious sounds were present over both lungs. The liver edge extended below the costal margin and was sensitive to touch. The blood pressure was 112 mm. systolic and 84 mm. diastolic, a relatively normal reading consistent with a state of chronic cor pulmonale. She weighed 109 pounds, a loss of 28¼ pounds within the last year.

Her first chest roentgenogram of November 2, 1948 showed a diffuse miliary nodulation throughout both lung fields. The hilar shadows were enlarged.

Her last chest roentgenogram taken fifteen months later (figure 3, February 8, 1950) showed small rarefied areas in the upper portions of the lung fields. All lobes were densely packed with miliary nodular densities. The horizontal interlobar septum became elevated

FIG. 3. Case 8. February 8, 1950. Diffuse miliary nodulation. Cor pulmonale.

to the level of the second right anterior intercostal space. The right ventricle was markedly enlarged. The outline of the diaphragm was irregular.

Course: The patient was still partly ambulatory. Two days later, on the morning of February 10, she complained of a sharp pain in the right chest and coughed up dark blood clots. She received a sedative, fell asleep, and ceased to breathe.

Post-Mortem Examination[3]

Macroscopic examination: The left lung weighed 890 gm. Its surface was studded with hyaline-like nodules, ranging in size from 1 to 3 mm. A few blebs were present along the borders of the lung. Both lobes were packed with sandlike nodules less than 1 mm. in size. The right lung weighed 880 gm. All three lobes showed extensive fine nodulation. The hilar lymph nodes were enlarged and included units measuring 3 cm. in diameter. The muscle of the right ventricle was 8 mm. thick, the muscle of the left ventricle was 1.3 cm. thick. The spleen and liver were slightly enlarged.

[3] Performed on February 11, 1950 by Dr. Harrison S. Martland.

Microscopic examination: The lungs were diffusely infiltrated with typical beryllium nodules consisting of noncaseating centers surrounded by lymphocytes, monocytes, numerous giant cells, and fibrosis. Numerous conchoidal inclusion bodies were present within and outside of the giant cells (figures 4 and 5). The heart showed hypertrophy of the right ventricle and slight acellular scarring. The tracheal lymph nodes showed fibrosis with beryllium granulomas containing giant cells and inclusion bodies. The spleen and liver revealed chronic passive congestion with atrophy of liver cells around central veins. Lymphocytic foci and a rare small granuloma with giant cells were found in the periportal space.

FIG. 4. Case 8. Discrete beryllium granulomas.

Spectrographic analysis by two laboratories revealed:

Laboratory 1.	Wet lung tissue—78.5 gm.	beryllium—0.6 γ
	Liver—100 gm.	beryllium—less than 0.1 γ
	Kidney—100 gm.	beryllium—less than 0.1 γ
	Spleen	no beryllium detected.
Laboratory 2.	Wet lung tissue—100 gm.	beryllium—less than 0.09 γ

Comment: This patient had been exposed to beryllium for fourteen years in the mounting and spray departments of radio tube factories. The amounts of beryllium recovered from her lung tissue by the two laboratories differed considerably, apparently also due to varying concentrations of the metal in different portions of the lungs. Her illness resulted in marked enlargement of the right ventricle. The survival period in this case could probably have been prolonged by administration of oxygen.

Case 9. The patient, H. C., was a 35-year-old, unmarried, white woman who was first examined by the writer on February 9, 1950. She had been given oxygen constantly since June 1949 and had been sitting up during most of the day and night, unable to breathe in a recumbent position.

The patient's present illness began in 1944 during her ninth year of work on radio tubes. At that time she developed shortness of breath. She also noticed swelling of her right knee. She received treatments for arthritis, and her tonsils were removed in August 1944. The difficulty in breathing persisted and was accompanied by palpitation of the heart. Treatments for rheumatic heart disease brought no relief. In April 1948 she became totally disabled. Her first chest roentgenogram was taken in May, and her illness was diagnosed as beryllium granulomatosis. In September, pneumoperitoneum was induced; the air injections seemed to aggravate her breathing. The refills were abandoned in June 1949, when it became difficult to find a free peritoneal space. Since then she continued on oxygen, constantly, using up a tankful daily. Her menstrual periods were absent for more than one year. Her weight went down from 142 pounds to 78.

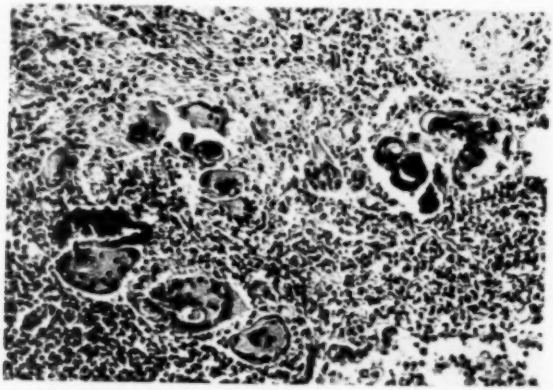

FIG. 5. Case 8. Section from lung showing beryllium granuloma. Note lymphocytic and monocytic infiltration, fibrosis, giant cells, and inclusion bodies.

Occupational exposure: The patient left school at the age of seventeen. On October 30, 1935, she obtained employment in a radio tube factory and continued there for twelve and one-half years. During the first year her work involved no dust exposure. In September 1936 she was transferred to the filament floor and worked there steadily until April 22, 1948, when she became totally disabled. Her place of work was located within five feet from the spray booths where the cathodes and hook wires were being coated. She was engaged in setting up the cathodes and hook wires for the conveyor and in unloading them after they have been coated. She also had to clean the racks and clips used in holding the cathodes and hooks. She operated the spray guns whenever the regular sprayer was absent. The air was filled with pulverized cathode coating scattered by the spray guns. The dustiness became still heavier during the cleaning of the spray booths, racks, and clips, when the dried coating was being scraped off and removed with a blower. No protection was provided against dust inhalation.

Clinical studies: The patient (figure 6) was very weak and could not stand up unassisted. Any change of position provoked coughing. She was emaciated and her breathing under oxygen was rapid and labored. The fingers were clubbed and the nails were curved downward. There was a pronounced hirsutism. A patchy pigmentation had been spread-

ing over the anterior chest wall. The pulse rate was 108 per minute, regular. The second pulmonic sound was markedly accentuated. Adventitious sounds were present over both lungs. The liver edge was felt below the costal margin. The ankles were edematous.

Her first chest roentgenogram of May 14, 1948 showed a diffuse miliary nodulation overshadowing both lung fields. A thickened horizontal interlobar septum and an accessory inferior one were visualized in the right lung field. The right ventricle was enlarged.

A bedside chest roentgenogram, twenty-one months later (figure 7, February 11, 1950) showed giant multilocular air pockets and numerous smaller blebs in the upper portions

FIG. 6. Case 9. Note emaciation, hirsutism, and patchy pigmentation.

of both lung fields. There was further enlargment of the right ventricle and of the root shadows.

The last chest roentgenogram of July 12, 1950 showed no essential changes. The urine was negative for beryllium.

Course: The state of agony continued with frequent paroxysms of coughing, during which the patient seemed to be gasping for her last breath. On November 17, 1950, she was placed on cortisone treatments. She received 200 mg. of Cortone daily for four days and 150 mg. on the fifth day. On the sixth day, in the evening, she developed a sudden sharp pain in the left chest. She complained of inability to breathe and died within two hours.

Post-Mortem Examination[4]

Macroscopic examination: The right pleural cavity was practically obliterated by adhesions. On the left there was a pneumothorax with adhesions to the upper lobe. Giant bullae and numerous smaller blebs were present in the upper lobes of both lungs. All lobes were filled with fine nodules. A terminal bronchopneumonia developed in the lower lobe of the right lung (figure 8).

The muscle of the right ventricle was 9 mm. thick; the muscle of the left ventricle was 8 mm. thick. Massive lymph nodes were present in both hilar regions and along the upper part of the abdominal aorta. The spleen and liver were enlarged and were held by adhesions to the diaphragm.

Microscopic examination: The lungs showed a widespread granulomatous reaction which consisted of fine nodules, diffuse fibrosis, and areas of emphysema. The granulomas

FIG. 7. Case 9. February 11, 1950. Bilateral giant blebs; diffuse nodulation; cor pulmonale.

contained many giant and round cells, few or no polymorphonuclears, many conchoidal inclusion bodies. The intervening tissue in the giant blebs showed metaplasia of alveolar epithelium. There were areas of suppurative bronchopneumonia. The muscle fibers of the right ventricle were hypertrophied. The liver showed marked chronic passive congestion, with distention of capillaries and central necrosis. An occasional small granuloma containing giant cells was found in the periportal space.

Spectrographic analysis:

Wet lung tissue—100 gm.	beryllium—less than 0.09 γ
Liver, kidney, and spleen—160 gm.	beryllium—0.11 γ

Comment: This patient had been exposed to beryllium in the cathode spray department for eleven and one-half years. The amount of beryllium demon-

[4] Performed on November 23, 1950 by Dr. Harrison S. Martland.

strated in her lung tissue was rather small. A significant amount of beryllium was present in the abdominal organs. The illness in this case resulted in marked enlargement of the right ventricle. The survival period was probably prolonged by early administration of oxygen. The hirsutism and the patchy pigmentation of the skin resulted apparently from prolonged amenorrhea.

Case 10. The patient, J. C., was a 40-year-old, married, white woman who was first examined by the writer on December 7, 1950.

The present illness had begun in 1941, two years after she had stopped working on radio tubes. At that time she complained of general weakness and shortness of breath. She attributed her condition to repeated miscarriages. In the winter of 1942 she was confined

FIG. 8. Case 9. Bilateral giant blebs; ruptured left lung.

to bed for four months and was treated for bronchial asthma. Repeated chest roentgenograms and sputum tests were negative for tuberculosis. Continued treatments for asthma brought no relief. In September 1950 her condition was diagnosed as beryllium granulomatosis. Corticotropin (ACTH) treatments produced no apparent improvement of her lung ailment.

She was married in 1934 and during the period from 1935 to 1944 she had one abortion and six miscarriages.

Occupational exposure: The patient began to work on radio tubes at the age of nineteen and had been employed in three different factories for ten years, from 1929 until May 1939. In each of the three factories she was engaged in assembly work, which included mounting of cathodes, grids, and micas. The mounting operation caused some of the filament coating to come off, spreading a fine dust. Inhalation of the coating dust provoked itching of her nose and sneezing.

Clinical and laboratory studies: The physical examination revealed slight cyanosis. The respiration at rest was 24 per minute. The pulse rate was 88 per minute. The blood pressure was 98 mm. systolic and 74 mm. diastolic. She was 59 inches tall and weighed 117½ pounds. Her vital capacity was 1,650 cc. Occasional adventitious sounds were present over both lungs.

Her first available chest roentgenogram of July 2, 1947 showed a diffuse network of large nodular densities. Miliary nodules were scarce. The hilar shadows were enlarged. The outline of the diaphragm was irregular.

Her last chest roentgenogram (figure 9, December 7, 1950) showed no changes in the pattern of the nodulation. The pleura over the upper portions of the lungs was thickened. A giant bleb appeared in the basal portion of the left lung. The heart shadow remained normal.

FIG. 9. Case 10. December 7, 1950. Diffuse nodulation; giant bleb in left lower lung field.

The electrocardiogram of December 10, 1950 showed no significant deviations from the normal.

Comment: This patient had been exposed to beryllium for ten years in her work on cathode parts of radio tubes. Her illness became stabilized without causing enlargement of the right ventricle. A longer survival period could be expected in this case.

The following reports on 4 cases are presented through the courtesy of Dr. Martin Castellano.

Case 11. The patient, M. B., was a 33-year-old, married, white woman. She became aware of increasing difficulty in breathing during the summer of 1946. Later on, she complained of wheezing, cough, fatigue, and weight loss.

She had been working in a radio tube factory for eleven years.

The physical examination on April 6, 1947 revealed a moderate cyanosis. The blood pressure was 100 mm. systolic and 58 mm. diastolic. Her weight was 106 pounds, a loss of 8 pounds since the beginning of the illness.

The chest roentgenogram (figure 10, April 6, 1947) showed a dense granular haziness overshadowing the lung fields. The root shadows were enlarged. The costophrenic areas were hyperaerated. The horizontal interlobar septum was visualized at the level of the third right anterior intercostal space.

A chest roentgenogram taken sixteen months later showed some clearing of the haziness. The horizontal interlobar septum became more elevated. The heart shadow remained normal.

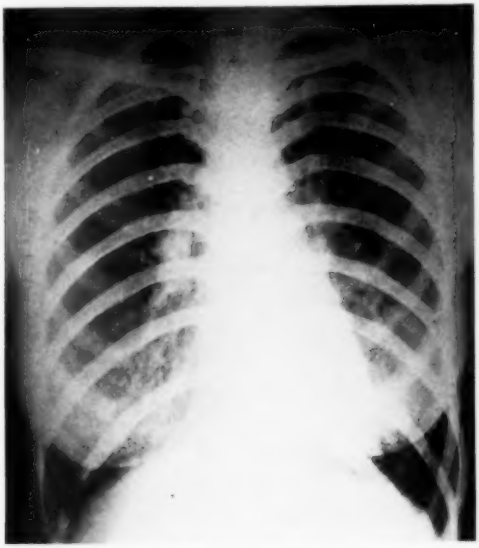

FIG. 10. Case 11. April 6, 1947. Diffuse granular haziness.

Case 12. The patient, H. K., was a 41-year-old, married, negro woman. She began to complain of shortness of breath in 1946.

She had been working in a radio tube factory from 1942 until 1945.

The physical examination on February 20, 1950 revealed severe shortness of breath. Her blood pressure was 100 mm. systolic and 78 mm. diastolic. The weight was 96 pounds, a loss of 32 pounds since she had become ill.

The chest roentgenogram (figure 11, February 20, 1950) showed a miliary nodulation throughout both lung fields. The upper portions of the latter were hyperaerated; the lower portions were densely packed with tiny nodules. The horizontal interlobar septum was lowered to the level of fifth right anterior intercostal space, indicating distention of the upper lobe. The hilar shadows and both ventricles were enlarged.

The patient died in April 1950. No autopsy was obtained.

Comment: The occupational histories in Cases 11 and 12 failed to indicate the dust-producing operations in which these 2 patients had been engaged.

Case 13. The patient, J. C., was a 36-year-old, married, white woman. She first noticed shortness of breath in 1946, soon after she stopped working on radio tubes. She had been working for thirteen years as a mounter in one radio tube factory.

The physical examination on March 29, 1949 revealed occasional wheezing over both lungs. The blood pressure was 124 mm. systolic and 80 mm. diastolic. There was no weight loss.

The chest roentgenogram (figure 12, March 29, 1949) showed a network of large nodular densities throughout both lung fields. Minute nodules were scarce. The heart shadow appeared to be normal.

A chest roentgenogram taken ten months later showed no changes.

FIG. 11. Case 12. February 20, 1950. Upper portions of lung fields hyperaerated, lower portions packed with minute nodules; both ventricles enlarged.

Comment: This patient had been exposed to beryllium for thirteen years in her work on radio tubes as a mounter. When last seen in 1950, she showed no evidence of a developing cor pulmonale. The granulomatous reaction appeared to be stabilized in this case, and a longer survival period could be expected.

Case 14. The patient, A. McB., was a 39-year-old, married, white woman. She became aware of difficulty in breathing during the early part of 1949, two and one-half years after she had stopped working in radio tube factories. She had been engaged for more than six years in cutting coated filament wire in two factories.

The physical examination on December 13, 1949 revealed cyanosis and marked shortness of breath. Several months later, the patient developed a left-sided spontaneous pneumothorax which had to be aspirated.

The chest roentgenogram (figure 13, February 29, 1950) showed a diffuse network of nodular densities overshadowing both lung fields. The upper half of the right lung was

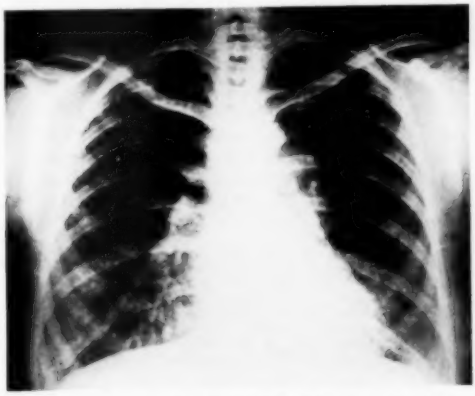

FIG. 12. Case 13. March 29, 1949. Diffuse nodulation.

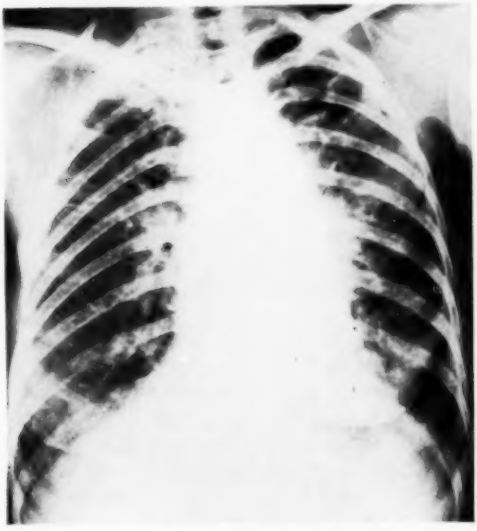

FIG. 13. Case 14. February 29, 1950. Diffuse nodulation; giant bleb in left upper lung field.

retracted, with a resulting narrowing of the intercostal spaces and elevation of the interlobar septum to the level of the second rib anteriorly. A giant bleb was present in the

apex of the left lung. The left border of the heart shadow was straightened. The root shadows were enlarged.

The patient died on October 18, 1950.

Post-Mortem Examination[3]

Macroscopic examination: There was a small amount of clear fluid in both pleural cavities and a moderately increased amount in the pericardial cavity. Old firm adhesions were present over the apices of the lungs. The hilar lymph nodes were enlarged. The muscle of the right ventricle was 1 cm. thick; the muscle of the left, 1.2 cm.

Microscopic examination: Microscopic examination of the lung tissue revealed fibrosis and noncaseating granulomas with epithelioid centers and numerous giant cells. Inclusion bodies were rare. There were interstitial emphysema and pulmonary edema. The spleen showed stasis. One small granuloma was found in a section from the liver.

Spectrographic analysis:

Wet lung tissue—71.5 gm. ..... beryllium—0.8 γ

Comment: This patient had been exposed to beryllium for more than six years in her work of cutting coated filament wire in radio tube factories. Her illness resulted in enlargement of the right ventricle.

DISCUSSION

The details of exposure to beryllium experienced by the patients in this series are as follows. Beryllium compounds had been used in the manufacture of radio tubes as an ingredient in the coating of cathodes, hook wires, and filaments. Several operations were accompanied by dispersion of beryllium dust through the surrounding air. The workers were not provided with respiratory protective equipment.

A view of the cathode-coating operation in a radio tube factory is presented in figure 14. The sprayer, patient N. Y. (Case 3), is operating two automatic spray guns. The racks loaded with cathodes or with hook wires are brought by a conveyor into the spray booth, an exhaust hood wide open on the side facing the guns. A heating unit is located beneath the hood to speed up the drying of the coating. Although the place had been tidied up before being photographed, the white coating mixture is seen spattered all over. The ripped rubber glove on the left hand of the operator is thickly covered with dry coating, and white specks are seen in her hair and on her arms.

Cleaning of the spray booths and of the racks and clips holding the cathodes and hook wires had been done at regular intervals by scraping off the spattered dried coating with a buffing wheel or with hand files. The dust was then removed with a blower, a hose connected with compressed air (figure 14).

The cutting and nicking of coated filaments by a drum-cutter caused scattering of fine coating dust through the surrounding air.

The assembling and mounting operations produced considerable dustiness, as some of the filament coating was chipped and scraped off by these procedures. Thousands of units were handled daily by an individual worker.

Three patients (Cases 3, 4, and 9) had been working in the spray depart-

[3] Performed on October 18, 1950 by Dr. Harrison S. Martland.

ment. Five patients (Cases 2, 6, 8, 10, and 13) had been engaged in assembling and mounting operations. Two patients (Cases 7 and 14) had been working on cutting coated wires and filaments. The dust-producing operations in which the other 4 patients (Cases 1, 5, 11, and 12) had been engaged remain unknown.

Single twenty-four-hour samples of urine were examined spectrographically for beryllium in Cases 2, 3, 4, 6, and 9. All of the examinations were negative. It is possible that repeated urinalyses would have produced positive results in some of the cases (2).

The lung tissue was examined in Cases 1, 7, 8, 9, and 14, and beryllium was found in each of them. In these 5 cases no apparent relationship existed between the amounts of beryllium recovered and the extent of the pulmonary

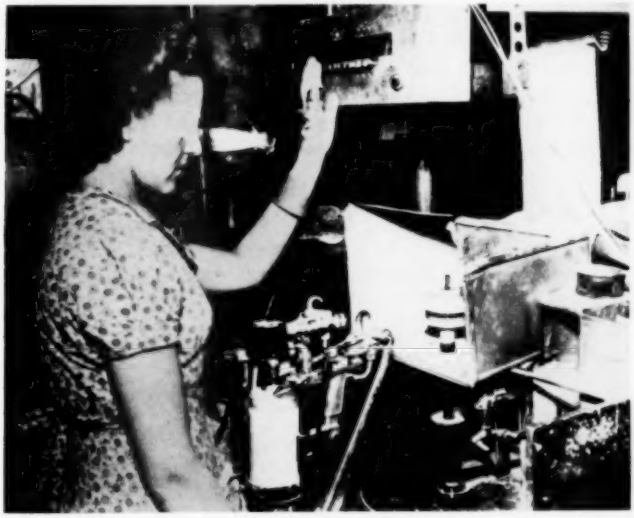

FIG. 14. Case 3. View of cathode coating operation.

involvement. Moreover, the results obtained by two laboratories in each of Cases 7 and 8 differed considerably. It is possible that the difference in the amounts of beryllium recovered by the two laboratories was due to varying concentrations of the metal in different portions of the lungs.

The liver, kidneys, and spleen were examined in Cases 8 and 9. In Case 8, beryllium was demonstrated in the liver and kidney. In Case 9, specimens of the three organs were examined jointly and considerable beryllium was found.

Multiple bleb formation was observed on roentgenographic examination in all cases. In Case 9, giant multilocular blebs and numerous smaller ones simulated cystic lung disease. In Cases 1, 10, and 14, solitary large blebs had the appearance of cavities. Rupture of blebs with a resulting pneumothorax occurred in Cases 1, 5, 9, and 14.

Electrocardiograms were obtained in Cases 3, 4, 6, and 10. In Cases 4 and 6, the findings indicated a developing cor pulmonale. In Cases 3 and 10, there were no significant electrocardiographic deviations from the normal, although the physical signs and roentgenographic evidence in Case 3 indicated enlargement of the right ventricle.

Chronic pulmonary beryllium granulomatosis is a grave, incurable disease. Due to lack of fever and pain, the patients in the present series sought medical advice when the ailment was far advanced and their difficulty in breathing became disabling. Even then some of them continued to be exposed to beryllium as there was a delay in recognizing the occupational nature of the illness. The expected survival period from the beginning of disability varied, depending on the condition of the heart. The outlook was more favorable in patients with a stabilized granulomatous reaction and no evidence of a cor pulmonale.

SUMMARY

Nine cases of chronic pulmonary beryllium granulomatosis are reported, with the results of post-mortem examinations in four. Details of exposure to beryllium dust in the manufacture of radio tubes are described.

SUMARIO

Granulomatosis Pulmonar Difusa en las Jóvenes Consecutivamente a la Exposición a los Compuestos Berílicos en la Fabricación de Tubos Radiofónicos

Los 9 casos comunicados son de granulomatosis pulmonar crónica por berilio, con hallazgos autópsicos en 4 de ellos. Ofrécense pormenores de la exposición al polvo de berilio en la fabricación de tubos radiofónicos.

RESUME

Granulomatose pulmonaire diffuse chez des jeunes femmes à la suite de l'exposition aux poussières de composés de béryllium, au cours de la fabrication de tubes pour la radio

Neuf cas de granulomatose pulmonaire chronique imputables au béryllium ainsi que les résultats de l'examen post-mortem, effectué dans quatre de ces cas, ont été rapportés. Les détails de l'exposition aux poussières de béryllium au cours de la fabrication de tubes pour la radio sont décrits.

Acknowledgments

Acknowledgment is made to Dr. Harrison S. Martland for his part in the studies of the cases and for the preparation of the photomicrographs; and to Dr. Martin Castellano for making available four of his cases.

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SIMULTANEOUS PULMONARY RESECTION AND THORACOPLASTY IN THE TREATMENT OF PULMONARY TUBERCULOSIS[1]

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INTRODUCTION

During the past ten years pulmonary resection has become an integral part of the treatment of pulmonary tuberculosis. Early in this period, pulmonary resection for tuberculosis was accompanied by formidable morbidity and mortality rates. Moore and his associates (1) reviewed the American literature up to May 1948, and found the operative mortality rate of the reported cases to be 15 per cent, the total mortality rate 26 per cent, and the incidence of spread or exacerbation of the tuberculosis to be 26 per cent. Empyema developed postoperatively in 12 per cent of the reported cases, and a bronchopleural fistula developed in 6 per cent. Sweet (2, 3) has reported discouraging results as determined on the basis of late follow-up studies of patients operated on without the benefit of streptomycin therapy.

In recent years several factors have resulted in a widening of the indications for resection and in an improvement in the early results following operations for pulmonary tuberculosis. These include advances in the techniques of thoracic surgery and anesthesia, the liberal use of whole blood, the introduction of antimicrobial therapy, and changing pathogenetic concepts of tuberculosis. Several reports (1, 4–9) have demonstrated a substantial reduction in morbidity and mortality accompanying the use of streptomycin and dihydrostreptomycin in conjunction with surgical measures, but sufficient time has not elapsed for the results of late follow-up studies to be reported.

Many thoracic surgeons working in this field agree that thoracoplasty should be performed in conjunction with pulmonary resection (10–13). Thoracoplasty is usually carried out three to six weeks after resection. When a thoracoplasty is performed, the pleural space is obliterated and the chances that postoperative empyema will develop are lessened. Furthermore, overdistention of the remaining lung is prevented and the risk of breakdown of residual caseous foci within the remaining lung is reduced. Many of the so-called postoperative spreads are in reality reactivations of quiescent foci present in the lung preoperatively but too small to cast a shadow on roentgenographic examination (2, 14). It will be remembered also that the discouraging late results reported by Sweet occurred in patients in the majority of whom thoracoplasty was not carried out. Overholt and his associates (10) report that ipsilateral exacerbations developed in only 16 per cent of patients with tuberculosis who underwent upper lobectomy, provided post-lobectomy thoracoplasty was carried out. Exacerbations appeared in 50 per cent of patients with no postoperative collapse therapy.

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Recently Iverson and Skinner (15, 16) have been performing pneumonectomy and thoracoplasty at the same operation. They reported on ten patients so treated, seven of whom were suffering from pulmonary tuberculosis. A bronchial fistula developed postoperatively in one case. There were no operative deaths. Conklin and co-workers (17) recently reported thirty-eight cases, in which thoracoplasty was combined with pulmonary resection, with one death. Samson (18) has performed fifty-five such operations, with one immediate and one late fatality. There were no major postoperative complications of consequence in his series. Others (7, 13, 19-22) have also indicated that such a combined procedure has been carried out in certain instances.

It seemed to the present writers that the combined procedure of pulmonary resection and thoracoplasty performed at the same operation offered certain ad-

TABLE 1

PATIENTS WHO UNDERWENT SIMULTANEOUS PULMONARY RESECTION AND THORACOPLASTY

PROCEDURE ASSOCIATED WITH THORACOPLASTY	PATIENTS	PATIENTS WITH POSTOPERATIVE COMPLICATIONS DUE TO TUBERCULOSIS	DISEASE OF 25 PATIENTS FOLLOWED 6 MONTHS OR MORE			
			Inactive	Apparently controlled	Arrested	Active
Pneumonectomy						
Right	5	1	2	1		1
Left	16	4	6	3	2	2
	21					
Lobectomy						
Left upper	5	1	1	1	1	
Right upper	4*	0	1	2		
Right upper and middle	5*	0	1	1		
	14					
Totals	35	6	11	8	3	3

* One patient also had a segmental resection of the superior division of the lower lobe.

vantages over a multiple-stage procedure in the operative treatment of pulmonary tuberculosis. Since 1947, the combined procedure has been carried out in selected cases at the Mayo Clinic. The results in these cases have been reviewed in an attempt to determine whether the risk of this extensive procedure is sufficiently small, and the early postoperative complications sufficiently infrequent, to warrant its use in selected cases.

MATERIAL

Thirty-five patients have undergone simultaneous pulmonary resection and thoracoplasty at the Mayo Clinic (table 1). There were 21 pneumonectomies, of which 16 were on the left and 5 were on the right. Fourteen patients underwent lobectomy; left upper lobectomy was carried out on 5 and right upper lobectomy

on 4. One patient on whom a right upper lobectomy was performed also had a segmental resection of the superior division of the right lower lobe. Five patients underwent right upper and middle lobectomy and one of these also had a segmental resection of the superior division of the right lower lobe. The 14 patients on whom lobectomy was carried out underwent a five-rib thoracoplasty at the time of pulmonary resection. One patient on whom pneumonectomy was carried out underwent a simultaneous six-rib thoracoplasty, 11 underwent a five-rib thoracoplasty, and 4 underwent a four-rib thoracoplasty. Only three ribs were removed initially in 5 patients, 3 of whom were operated on early in the series before experience with this combined procedure had accumulated. The condition of the other 2 patients at the time of operation required postponement of the completion of the thoracoplasty to a later date. Resection of further ribs was undertaken in all of these 5 patients. Two of the patients with a four-rib thoracoplasty and 2 with a five-rib thoracoplasty also underwent resection of further ribs at a later date.

Streptomycin or dihydrostreptomycin was used in all cases in the absence of drug-resistant organisms. Recently, para-aminosalicylic acid has been used in conjunction with dihydrostreptomycin. Positive bacteriologic evidence of the presence of tubercle bacilli was available in all cases but one. Pathologic evidence was available postoperatively in this case in support of the diagnosis. There were no desperate-risk cases in this group, the disease being well stabilized by the time of operative intervention. The disease had existed in the majority of patients for one to three and one-half years preoperatively. The longest preoperative duration of tuberculosis, according to the history, was twenty-three years and the shortest was nine months. Fifteen patients had evidence of bilateral tuberculosis roentgenographically, but in only 3 instances was the contralateral lesion considered to be active.

The indications for simultaneous thoracoplasty and pulmonary resection necessarily differ from the indications for resection alone. Failure of thoracoplasty, tuberculoma, and tuberculosis of a lower lobe are not considered indications for the combined procedure. Tuberculous endobronchial disease, either ulcerative or stenotic, was the primary indication for pulmonary resection and simultaneous thoracoplasty in 14 of the patients and a secondary indication in 5. Ten patients were operated on for apical cavitary disease, while 2 patients were operated on for a "destroyed lung." Failure of pneumothorax was considered the primary indication for surgical intervention in 7 cases and a secondary indication in 2. One patient was operated on for a bronchopleural fistula and tuberculous empyema, and another for empyema and an unexpanded lung.

TECHNIQUE

The routine method of preoperative and postoperative care as well as the operative technique employed will be outlined briefly. Usually the patients were transferred to the hospital from a sanatorium one to several days before operation and were started on treatment with dihydrostreptomycin. In certain cases a longer period of preoperative antibacterial therapy was necessary. The prin-

ciples followed in carrying out preoperative and postoperative antimicrobial therapy have recently been described (23).

At the time of operation the patient was placed in the lateral decubitus position. Under intratracheal gas, oxygen, and ether anesthesia a posterolateral incision was made and extended cephalad to a point above the level of the spine of the scapula to facilitate performance of the thoracoplasty. Pulmonary resection was carried out first. The bronchus was clamped and divided, the "cut and sew" technique (24) being used, and the vessels were ligated separately and divided. When necessary, decortication of the remaining lobe or lobes and parietal pleurectomy were carried out.

At the present time when upper or upper and middle lobectomy is performed, it is the practice to carry out a five-rib thoracoplasty, with resection of the first rib through the fifth, including portions of the cartilages of the first three ribs. Smaller segments of ribs four and five are removed so that the thoracoplasty is "tailored" to the requirements of the individual case. The ribs are removed down to, but not including, the transverse processes. In certain instances it may be permissible to leave the first rib in place.

Patients on whom a pneumonectomy is carried out likewise undergo a five-rib thoracoplasty. Further experience may prove, however, that a more extensive thoracoplasty may be advisable in these cases.

In the present series it was the customary practice to administer 1,000 cc. of blood during the operative procedure. A solution containing 240,000 units of penicillin was left in the pleural space, and one or two rubber catheters were left to drain the space for forty-eight hours.

Postoperatively, treatment with dihydrostreptomycin was continued and para-aminosalicylic acid added when it could be tolerated by the patient. Administration of both drugs was continued for a minimum of three months postoperatively. Chemotherapy for a longer period of time was given to those patients who had significant amounts of unresected tuberculous tissue. The patients were returned to the sanatorium two to four weeks after operation. A graduated program of physical activity was usually started after three months of complete rest in bed, and the patients were dismissed six months after operation to continue convalescence at home, if cultures and roentgenograms remained negative.

RESULTS

All of the patients withstood the operative procedure well, and with 2 exceptions no significant fall in blood pressure occurred during the procedure or in the postoperative period. In the case of 2 patients, the blood pressure became unobtainable on the operating table, but in each case the administration of blood restored the blood pressure to normal. No early deaths have occurred in this series. There was one late death five months after operation.

Method of follow-up observation: The method employed in following up these patients was the same as that described in another report (25). Clinical, bacteriologic, and roentgenographic follow-up studies were made when possible by

re-examination at the clinic. When this was not possible, letters from the patients and reports from their home and sanatorium physicians were used. Preoperative and postoperative roentgenograms of each patient were studied, including films made available by the patient's home and sanatorium physicians. In this manner adequate follow-up data were available on 25 patients six or more months postoperatively. In one of these cases a written report only of a follow-up roentgenogram was available. The remaining 10 patients have been operated on during the past six months.

Status of disease: In determining the status of the disease of the patients reported here, the terms *inactive*, *arrested*, and *active* have been employed as defined in the 1950 edition of the *Diagnostic Standards and Classifications* of the National Tuberculosis Association. The term *apparently controlled* is used to designate cases which should fall into the classifications *inactive* or *arrested* but lack sufficient bacteriologic data to permit this distinction.

The condition of 25 patients was followed for six months or longer, the longest follow-up period being forty-six months (table 1). The disease of 11 of these patients has been classified as inactive; of 8, as apparently controlled; of 3, as arrested; and of 3, as active. Of the remaining 10 patients, one has been lost to follow-up, one died five months postoperatively, and 8 are still hospitalized at the time of this writing. Three of these 8 have stable roentgenograms of the chest and negative cultural studies for tubercle bacilli four months after operation. The remaining 5 have been operated on too recently for evaluation but are convalescing satisfactorily. Thus, of 10 patients whose condition has been followed for less than six months after operation, one has died and the disease of the remaining 9 should be classified as "activity undetermined."

Postoperative complications: Postoperative complications due to tuberculosis developed in 6 patients (table 1). Three of these patients were known to be discharging streptomycin-resistant tubercle bacilli. The first of these 3 patients had a bronchopleural fistula, tuberculous empyema, a pleurocutaneous fistula, and a tuberculous wound infection, and died five months postoperatively. The second patient had a contralateral reactivation fourteen months postoperatively. The lesion resolved during treatment with neomycin, and the disease is now considered arrested. The third patient with streptomycin-resistant tubercle bacilli experienced a contralateral reactivation and tuberculous bronchitis in the stump six and eight months, respectively, after operation. The tuberculous bronchitis responded to antimicrobial therapy, but the contralateral lesion has remained active. One patient whose tubercle bacilli were known to be sensitive to streptomycin has continued to have tubercle bacilli in the sputum intermittently for two years postoperatively in spite of antimicrobial therapy. She is considered to have active disease. Whether or not the organisms were sensitive to streptomycin was unknown in 2 of the 6 cases in which postoperative complications developed. In one of these, a contralateral reactivation occurred three months postoperatively. This lesion responded to treatment, and the patient's disease is now arrested. The other patient experienced a contralateral reactivation forty-two months after operation and still has active disease. Thus, of 6 patients known

to have had tuberculous complications, one has died, the disease of 3 remains active, while that of 2 is considered arrested.

COMMENT

In the opinion of the writers, it is advisable to perform a thoracoplasty when upper lobectomy, upper and middle lobectomy, or pneumonectomy is indicated in the treatment of pulmonary tuberculosis. When thoracoplasty is combined with pulmonary resection, overdistention of the remaining pulmonary tissue is prevented and the dead space is obliterated. The likelihood of reactivation of the remaining foci of disease and of the development of empyema is thereby reduced.

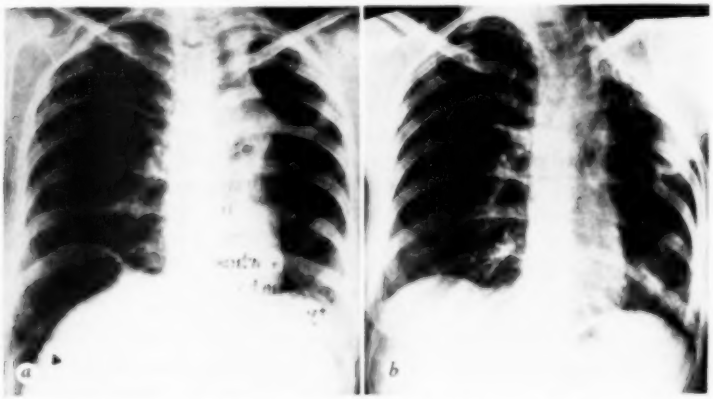

FIG. 1. Roentgenograms of the thorax of a patient with bilateral apical tuberculosis. A tension cavity is present in the left upper pulmonary field. (*a*). Preoperative appearance. (*b*). Fifteen months after simultaneous left upper lobectomy and removal of ribs one through five. There is minimal scoliosis, lack of mediastinal shift, and lack of overdistention of the remaining pulmonary tissue.

It is further believed that certain advantages accompany the simultaneous performance of these two procedures. The added risk of a second operation is avoided and the patients do not face the added mental and financial burden of two operative procedures. As mentioned previously, when thoracoplasty is performed at the same time as pulmonary resection, the dead space is obliterated early and overdistention of remaining pulmonary tissue is prevented. When thoracoplasty is postponed for several weeks some overdistention is bound to occur, and the collapse afforded after the remaining pulmonary tissue has become adherent and stiff may not be as effective in the prevention of either empyema or overdistention. Furthermore, the simultaneous performance of these two procedures may allow the preservation of more pulmonary tissue than might otherwise be possible. A minimally diseased lower lobe often can be saved

if the protection afforded by immediate thoracoplasty is available before the lobe has become overdistended and adherent. Thoracoplasty done at the time of pulmonary resection need not be as radical as the usual thoracoplasty, and deformity and disability are thereby reduced (figure 1). If thoracoplasty is carried out first and pulmonary resection later, some of these advantages apply but the disadvantages which accompany the performance of two separate operative procedures are present. Furthermore, the dissection for pulmonary resection is made more difficult when thoracoplasty is carried out as an earlier operation.

The data presented here indicate that no undue risk accompanies the simultaneous performance of pulmonary resection and thoracoplasty. Neither do the complications seem excessive. The disease of the vast majority of the patients who have been followed for a sufficient time falls into one or another of the categories *inactive*, *apparently controlled*, and *arrested*. Many of these patients are gainfully employed for the first time after years of hospitalization. Sufficient late follow-up studies are not available to allow any statement regarding long-term results. The fact that one patient experienced a reactivation forty-two months postoperatively re-emphasizes the fact that these patients should not be considered cured. All but two of the complications occurred after left pneumonectomy but this is of doubtful significance since almost half of the procedures in this series were left pneumonectomies.

It should be emphasized that all of the patients of the present report were in good condition; hence the operative risk was minimal. The combined procedure would not be considered advisable for poor-risk patients. Nevertheless, bilateral disease per se does not constitute a contraindication. In fact, the presence of a contralateral lesion may add to the indications for performing the two procedures simultaneously to ensure immediate prevention of overdistention and to decrease the likelihood of reactivation or extension of the known residual disease.

SUMMARY

Simultaneous pulmonary resection and thoracoplasty for pulmonary tuberculosis is a safe procedure for "good-risk" patients. In a series of 35 cases there were no operative deaths and only one late death. The condition of 10 of the patients including the one who died has been followed for less than six months. Of the remaining 25 whose condition has been followed six to forty-six months, the results are satisfactory in 22 while 3 patients still have active tuberculosis. Tuberculous complications developed in 6 patients; one of these died, 3 still have active disease, and 2 are now classified as arrested.

This combined procedure is recommended as the measure of choice for "good-risk" patients when upper lobectomy, upper and middle lobectomy, or pneumonectomy is indicated in the treatment of pulmonary tuberculosis. The patient is spared the added risk, worry, and financial burden of two operations. Overdistention of residual pulmonary tissue is prevented early before the tissues become adherent and stiff. Pulmonary resection and thoracoplasty may be less radical when performed together than when performed separately, resulting in less deformity and disability.

SUMARIO

La Resección Pulmonar y la Toracoplastia Simultáneas en el Tratamiento de la Tuberculosis Pulmonar

En la tuberculosis pulmonar la toracoplastia y la resección pulmonar simultáneas constituyen un procedimiento seguro en los enfermos que representan buenos riesgos. En una serie de 35 casos, no hubo mortalidad operatoria y sólo hubo una muerte tardía. El estado de 10 de los enfermos, incluso el fallecido, ha sido observado durante menos de seis meses. De los otros 25 mantenidos en observación de seis a cuarenta y seis meses, los resultados son satisfactorios en 22, mientras que 3 tienen todavía tuberculosis activa. En 6 se presentaron complicaciones tuberculosas, y uno de éstos ha muerto, 3 tienen todavía la enfermedad en forma activa, y 2 han sido clasificados como estacionados.

Recomiéndase ese procedimiento combinado como medida de elección en los tuberculosos pulmonares que constituyen buenos riesgos cuando están indicadas en el tratamiento la lobectomía superior, la lobectomía superior y media o la neumonectomía. Ahórrase así al enfermo el mayor riesgo, preocupación y gravamen económico de dos operaciones. Impídese también a tiempo la hiperdistensión del tejido pulmonar residual antes de que el mismo se adhiera y atiese. La resección pulmonar y la toracoplastia pueden resultar menos radicales cuando se ejecutan juntas, yendo seguidas de menos deformidad e incapacidad.

RESUME

Résection pulmonaire et thoracoplastie simultanées dans le traitement de la tuberculose pulmonaire

La thoracoplastie accompagnée d'une réseccion pulmonaire est un procédé qui n'offre pas de danger chez les sujets représentant un "bon risque" opératoire. Dans une série de 35 cas opérés, la mortalité opératoire a été nulle, un des malades a succombé plus tard. Dix de ces malades, y compris le malade qui a succombé, ont été suivis pendant moins de six mois. Parmi les 25 autres malades du groupe, dont la surveillance a été poursuivie pendant six à quatorze mois, les résultats se sont montrés satisfaisants chez 22 d'entre eux, les 3 autres continuent à présenter des lésions actives. Des complications tuberculeuses se sont développées chez 6 malades, l'un d'eux est mort, 3 ont encore une tuberculose en activité, chez 2 la tuberculose est considérée comme arrêtée.

Ce procédé opératorie mixte est recommandé comme la méthode de choix dans le traitement de la tuberculose pulmonaire, quand il y a lieu de procéder à l'exérèse, soit du lobe supérieur, soit du lobe supérieur et du lobe moyen, ou lorsqu'une pneumoectomie est indiquée. Le double risque opératoire, les soucis et la charge financière de deux interventions sont ainsi épargnés au malade. Des mesures sont prises pour éviter la surdistension du tissu pulmonaire résiduel avant que ces tissus ne deviennent adhérents et scléreux. La résection pulmonaire et la thoracoplastie pratiquées simultanément peuvent être moins radicales ce qui réduit l'importance des déformations et de l'invalidité.

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THE PROGNOSIS OF TUBERCULOUS MENINGITIS[1,2]

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Tuberculous meningitis can be cured by streptomycin. At the Clinique des Enfants Malades alone, 127 children admitted between January 1947 and November 1949 have completed treatment and have been discharged with the diagnosis of "tuberculous meningitis" written on their charts. Are these apparent recoveries no more than temporary remissions of this illness? Let us examine this question.

In February 1950 we presented the results of treatment in our patients with tuberculous meningitis to the Experts Committee of UNICEF[3] and WHO[4]. The results were concerned with 262 cases. At the time of presentation the number of survivors was as follows:

27 children admitted in 1947 (before September 1)
66 children admitted in 1947–1948 (September 1947 to September 1948)
40 children admitted in 1948–1949 (September 1948 to November 1, 1949).

Today (February 1951), one year later, in the third series (the most recent), 5 children are dead. Four of them were still being treated when the previous statistics were compiled. The fifth died from a relapse.

In the second series, one child died from relapse; the 65 others are doing well.

The 27 children of the first series are doing well, with a follow-up of more than three years and five months.

Thus, it seems definite that tuberculous meningitis can be cured; but in what percentage of cases does permanent cure take place?

These 127 children, alive February 1, 1951, are the survivors of a group of 262 cases of tuberculous meningitis. Nearly one-half of the patients survived with streptomycin therapy; approximately one-half died in spite of the treatment, 90 per cent of these in the first six months.

Could either of these outcomes be predicted on admission; or are the different types of treatment responsible for the different evolutions? In order to be able to evaluate the different modes of treatment and to choose the proper form for an individual patient, we must first know more of the clinical factors of good or bad prognosis.

Age: The first factor of importance in prognosis is the age of the patient. This information is of importance in attempting to compare the results obtained in one

[1] Based on a study from the Clinique Medicale des Enfants, Paris, France, by R. Debré and H. E. Brissaud, with the collaboration of L. Nicolas for the clinical part, of H. Noufflard, P. Canlorbe, and M. Cousin in bacteriology, and of A. Lerique and S. Balsan in electroencephalography.

[2] Lecture delivered before Department of Pediatrics, New York Hospital—Cornell Medical Center, on February 17, 1951.

[3] United Nations International Children's Emergency Fund.

[4] World Health Organization.

clinic with those of another. Some hospitals do not admit infants or, if they do, they take them in different proportions in relation to the admissions of children or adults. The results of the treatment of tuberculous meningitis vary greatly indeed according to age.

In our own series, there was a very high mortality rate in children less than one year old (12 of 16, or 75 per cent), while in patients from six to twenty years of age the mortality rate was approximately 37.5 per cent (48 of 128; table 1).

The higher mortality rate for those less than eighteen months old may be a result of late diagnosis. It is difficult to recognize the early symptoms and the change in state of consciousness. The increased intracranial pressure may give rise to few symptoms because of the softness of the skull. An enormous hydrocephalus is usually present when the diagnosis of tuberculous meningitis is made in an infant.

Thus, the severe prognosis in infants may well be due to the fact that there is a high incidence of two important factors of bad prognosis: widespread tuberculous lesions and, more important, severe pathologic changes in the meninges when the treatment is started.

TABLE 1

PROGNOSIS ACCORDING TO AGE

AGE	NUMBER OF CASES	DEAD	ALIVE	MORTALITY
				per cent
6 to 20 years	128 (49%)	48	80	37.5
1 to 6 years	118 (45%)	69	49	58
< 1 year	16 (6%)	12	4	75

Type of tuberculosis: Tuberculous meningitis can occur in the course of any primary tuberculosis, but it is exceptional in the simplest forms, while it is a usual complication of acute miliary tuberculosis. Though meningitis is more frequent in association with miliary tuberculosis, is it more severe in these circumstances?

The type of exposure to tuberculous infection has been estimated in 256 cases of our series as follows:

Heavy exposure—40 cases; 22 dead (55 per cent)
Known but episodic exposure—34 cases; 14 dead (41 per cent)
Unknown exposure—182 cases; 89 dead (51 per cent).

These results do not show any clear correlation between the type of exposure and the prognosis.

A special case is that of exposure to a patient treated with streptomycin. We have seen the following case:

The patient was a 5-year-old girl admitted to the hospital on October 17, 1949. On admission she was perfectly conscious. Examination of the cerebrospinal fluid revealed 240 cells per cu. mm., 260 mg. of protein per 100 cc., sugar concentration too low to measure. Tubercle bacilli were found on direct examination of the fluid.

The child's illness rapidly progressed, and she died on November 9.

The treatment had been: 1 gm. of streptomycin per day intramuscularly; 25 mg. intrathecally, first by lumbar and then by ventricular routes.

Culture positive for *M. tuberculosis* was found on admission and also on October 28. Sensitivity to streptomycin of both strains was tested. The first one was resistant between 1 and 2 γ per cc.; the second one between 5 and 10 γ per cc. Resistance to bactericidal action of streptomycin was more than 1,000 γ per cc.

Two months before her primary tuberculosis, this child had been in contact with a patient with tuberculous cavitations of the lung who had been treated with streptomycin.

Duration of the primary tuberculosis at the occurrence of the meningitis: Meningitis is, in most cases, an early complication of primary tuberculosis. This is shown once more in table 2, but the results of the treatment cannot be said to be better or worse for the 37 patients who had meningitis long after primary tuberculosis.

On the other hand, it should be emphasized that the mortality rate has been 40 per cent when the primary tuberculosis has been recognized against 60 per

TABLE 2

PROGNOSIS ACCORDING TO TIME ELAPSED SINCE PRIMARY TUBERCULOSIS AT THE ONSET OF MENINGITIS

SINCE PRIMARY TUBERCULOSIS	NUMBER OF CASES	DEAD	ALIVE	MORTALITY
				per cent
Less than 3 months	93 (36%)	41	52	
3 months to 1 year	36 (22%)	16	20	40
More than 1 year	37 (22%)	14	23	
Unknown	96	58	38	60

cent when it has not. This may be explained by an earlier diagnosis of tuberculous meningitis in the former group.

Coexistence of miliary tuberculosis: When the roentgenogram and examination of the ocular fundi have shown the existence of a widespread miliary tuberculosis in association with meningitis, the mortality rate has been significantly higher than the over-all mortality rate of 50 per cent.

Early diagnosis of the meningitis: The treatment of tuberculous meningitis will be effective only if started early.

This is shown by: (a) the time elapsed since the first clinical signs and (b) the condition of the child.

In 232 of 262 cases, the first signs of the disease started abruptly enough to allow the very day of the clinical onset to be fixed (table 3).

In most cases, 115 of 232, the diagnosis was made and the treatment started in the second week of illness. Of these 115 children, 54 died (nearly 50 per cent). In 38 cases the treatment was started in the third week and the mortality rate was higher, nearly 66 per cent. In 79 cases, on the other hand, the treatment could be started as early as the first week. Twenty-three children died, a mortality rate

of approximately 33 per cent. These are significant differences and show how much the success of therapy depends upon the speed with which the diagnosis of tuberculous meningitis is established.

State of consciousness: The course of the tuberculous meningitis, though regular as a whole, can be long or short; and there is not always a correlation between the duration of illness at the time of the diagnosis and the condition of the child on admission to the clinic. Some children are already comatose despite an illness of only a few days, while others are still perfectly conscious after two weeks. The bearing of the state of consciousness at the time of admission to the hospital on the mortality rate is much more impressive than that of the duration of illness at the beginning of treatment.

TABLE 3

PROGNOSIS ACCORDING TO DATE OF TREATMENT

DATE OF TREATMENT	NUMBER OF CASES	DEAD	ALIVE	MORTALITY
				per cent
First week	79 (33%)	23	56	30
Second week	115 (43%)	54	61	45
Third week	38 (14%)	23	15	60

TABLE 4

PROGNOSIS ACCORDING TO STATE OF CONSCIOUSNESS

STATE OF CONSCIOUSNESS	NUMBER OF CASES	DEAD	ALIVE	MORTALITY
				per cent
Complete consciousness	54 (21%)	15	39	27
Drowsiness	58 (22%)	19	39	33
Sleepiness	71 (27%)	37	34	52
Stupor	58 (22%)	39	19	67
Coma	21 (8%)	19	2	90

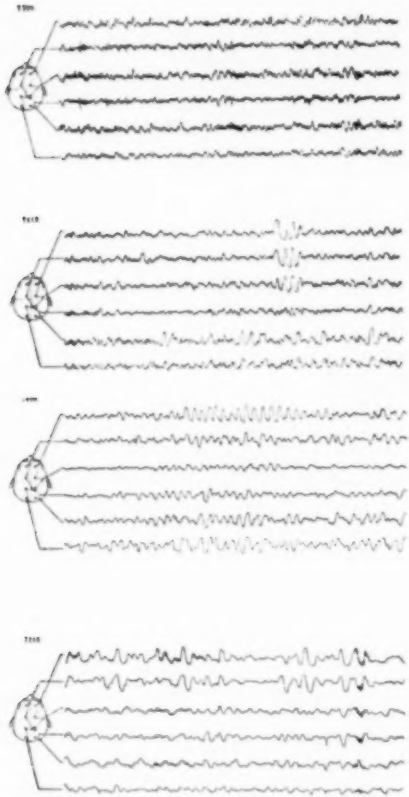
We have analyzed the therapeutic results in our series by different groups according to the state of consciousness of the child at the time of admission: *complete consciousness, drowsiness, sleepiness, stupor, coma* (table 4).

The results of this analysis are a good example of how different the potentialities of treatment are at present according to the stage of evolution of the disease when therapy is started. In the same department, the mortality varies from 27 to 90 per cent according to which one of these groups the patient belonged at the time of admission. Even between the group designated *drowsiness* and the one designated *stupor*, there was an enormous difference in the case fatality rates. There were 39 deaths and 19 survivals of the 58 children admitted in stupor; while, on the other hand, there were 19 deaths and 39 survivals of the 58 admitted in a state of drowsiness.

Electroencephalogram: There are gross differences in the changes of the electroencephalogram (EEG) from one patient to another and in the same patient from

one stage of illness to another. Moreover, the change in the records and the change in the state of consciousness are somewhat parallel.

We have tried to establish an objective classification in the degrees of changes in the electroencephalograms in order to evaluate their prognostic significance (figure 1).



Type I—Clear alpha rhythm, rare generalized delta waves of small amplitude.

Type II—High voltage delta waves, isolated or in generalized bursts. The dominant alpha rhythm remains clear.

Type III—No dominant rhythm. Many delta waves in numerous generalized bursts.

Type IV—Very slow unorganized waves of 1 to 3 cycles per second.

FIG. 1. Changes in the electroencephalogram. (The age of the patients: thirteen to fourteen years old.)

As shown in table 5, in 77 cases a first record could be made within the first ten days of treatment. In 43 patients, there were important changes in the EEG (type III or IV in our classification); 27 of these children died. In 34 patients there were no important changes in the EEG (normal, or type I or II); only 4 of these children died. The evolution of these changes in the electroencephalograms, as shown by serial recordings, gives very important information in each case (table 6).

It is interesting to compare the changes in the EEG with the clinical data. It can be seen in table 7 that, when there were important changes in the state of consciousness (stupor or coma = P_3 or P_4), there were important changes too in the EEG (type III or IV). The latter gives no more than confirmation of the obvious severity of a late case. When the changes in the state of consciousness are less marked, however, the EEG is sometimes very abnormal; and in these cases the mortality rate remains very high.

TABLE 5

PROGNOSIS ACCORDING TO INITIAL ELECTROENCEPHALOGRAM

(In the first 10 days of treatment)

INITIAL ELECTROENCEPHALOGRAM	NUMBER OF CASES	CLINICAL EVOLUTION		
		Dead	Treatment completed	Still under treatment
N	16	2	2	12
I	7	0	1	6
II	11	2	2	7
III	32	18	3	11
IV	11	9	1	1

TABLE 6

PROGNOSIS ACCORDING TO EVOLUTION OF THE ELECTROENCEPHALOGRAM

	TOTAL NUMBER OF CASES	FIRST ELECTROENCEPHALOGRAM	LATER ELECTROENCEPHALOGRAM	NUMBER OF CASES	CLINICAL EVOLUTION		
					Dead	Treatment completed	Still under treatment
First EEG normal, remains normal	18	N	N		1	7	10
Improvement	58	I	N	16	0	10	6
		II	N or I	18	1	8	9
		III	N or I or II	21	4 (7)	7 (26)	10 (25)
		IV	III	3	2	1	0
Deterioration	28	N	I or II	4	0	0	4
		N	III or IV	9	5	2	2
		I	III or IV	4	3 (19)	0 (2)	1 (7)
		II	III or IV	2	2	0	0
		III	IV	9	9	0	0

Let us study, for example, the group of 34 children whose state of consciousness has been called *drowsiness* (= P_1). Seventeen of these children had a normal or type I EEG and only one of these children died. The 17 others had a very altered EEG (type II, III, or IV), and 9 of these children died.

Let us now examine the group of 28 children considered as *sleepy* (= P_2). At the time therapy was started, 8 had a normal EEG, or a type I or II EEG, and they are all alive. Twenty had a very altered EEG (type III or IV), and 11 are dead.

This shows that the information given by the first EEG helps to make a better evaluation of the severity of the case.

Cerebrospinal fluid abnormalities: The changes in the cerebrospinal fluid increase during the first days of the untreated disease, at least the changes in the proteins, sugar, and chloride levels. This has been shown in some children who had several lumbar punctures before the treatment was started. While the cell

TABLE 7

PROGNOSIS ACCORDING TO STATE OF CONSCIOUSNESS AND INITIAL ELECTROENCEPHALOGRAM

STATE OF CONSCIOUSNESS	NUMBER OF CASES	TYPE OF FIRST ELECTROENCEPHALOGRAM	NUMBER OF CASES	CLINICAL EVOLUTION		
				Dead	Treatment completed	Still under treatment
N	6	N	2	1	0	1
		I	1	0	0	1
		II	0	0 (3)	0 (0)	0 (3)
		III	2	1	0	1
		IV	1	1	0	0
P_1	34	N	12	1	2	9
		I	5	0	1	4
		II	6	2 (10)	1 (5)	3 (19)
		III	10	6	1	3
		IV	1	1	0	0
P_2	28	N	2	0	0	2
		I	1	0	0	1
		II	5	0 (11)	1 (4)	4 (13)
		III	15	8	2	5
		IV	5	3	1	1
P_3	4	N	0	0	0	0
		I	0	0	0	0
		II	0	0 (3)	0 (1)	0 (0)
		III	2	1	1	0
		IV	2	2	0	0
P_4	5	N	0	0	0	0
		I	0	0	0	0
		II	0	0 (4)	0 (1)	0 (0)
		III	3	2	1	0
		IV	2	2	0	0

counts had sometimes decreased, the protein concentration was greater at the different examinations; the sugar and chloride concentrations were at lower levels.

Thus, the increase in proteins and the decrease in sugar and chloride give some information on the date of the diagnosis.

In tables 8 and 9 may be seen the mortality rate for the series according to the protein and sugar concentrations in the cerebrospinal fluid before the treatment was started.

When the total protein of the cerebrospinal fluid was more than 150 mg. per 100 cc., the mortality rate was approximately 60 per cent. When the protein was less than 100 mg. per 100 cc., the mortality rate was approximately 40 per cent.

The sugar concentration has proved to have similar correlation with the mortality rate (table 9). When the value for cerebrospinal sugar was less than 20

TABLE 8

PROGNOSIS ACCORDING TO INITIAL PROTEIN CONCENTRATION IN THE CEREBROSPINAL FLUID
(for 262 cases)

PROTEIN CONCENTRATION	NUMBER OF CASES	DEAD	ALIVE	MORTALITY
				per cent
Less than 100 mg. per 100 cc.	102 (39%)	42	60	40
100 to 150 mg. per 100 cc.	85 (29%)	41	44	50
More than 150 mg. per 100 cc.	75 (32%)	46	29	60

TABLE 9

PROGNOSIS ACCORDING TO INITIAL SUGAR CONCENTRATION IN THE CEREBROSPINAL FLUID
(for 73 cases)

SUGAR CONCENTRATION	NUMBER OF CASES	DEAD	ALIVE	MORTALITY
				per cent
More than 40 mg. per 100 cc.	31 (42%)	11	20	35
20 to 40 mg. per 100 cc.	27 (37%)	12	15	40
Less than 20 mg. per 100 cc.	15 (21%)	12	3	80

TABLE 10

PROGNOSIS ACCORDING TO SENSITIVITY TO STREPTOMYCIN (BACTERIOSTATIC LEVEL) OF THE STRAINS ON FIRST ISOLATION
(for 85 cases)

CONCENTRATION OF STREPTOMYCIN INHIBITING GROWTH	NUMBER OF CASES	DEAD	ALIVE	MORTALITY
				per cent
Less than 1 γ per ml.	72 (85%)	32	40	45
More than 1 γ per ml.	13 (15%)	11	2	85

mg. per 100 cc., the mortality rate was 80 per cent; while with a value for sugar of more than 40 mg. per 100 cc., the mortality was only 35 per cent.

Bacteriologic factors: On first isolation from the cerebrospinal fluid, the tubercle bacilli are susceptible to streptomycin but they vary in the degree of susceptibility (table 10). Seventy-two of 85 strains were inhibited by 1 γ or less of streptomycin per ml. in Tween-albumin medium. Thirteen strains required higher concentration of streptomycin for inhibition. Eleven of the corresponding pa-

tients died, while only 32 of the former group of 72 died. The significance of this bacteriologic factor appears even more clearly in the course of the treatment. The strains isolated subsequently have shown, as a rule, less sensitivity to streptomycin action (table 11). Only 21 of 49 strains were still inhibited by less than 1 γ of streptomycin per ml. Even in these cases, the mortality rate had increased to 57 per cent.

Strains from 28 patients were resistant to more than 1 γ, and the case mortality rate in this group was 85 per cent.

The strains isolated before treatment behave very differently when they are left for one month in the presence of streptomycin in Tween-albumin medium and are subsequently subcultured on Löwenstein egg medium. The inhibitory

TABLE 11

PROGNOSIS ACCORDING TO SENSITIVITY TO STREPTOMYCIN (BACTERIOSTATIC LEVEL) OF THE STRAINS ISOLATED IN THE COURSE OF TREATMENT

(for 49 cases)

CONCENTRATION OF STREPTOMYCIN INHIBITING GROWTH	NUMBER OF CASES	DEAD	ALIVE	MORTALITY
				per cent
Less than 1 γ per ml.	21 (43%)	12	9	57
More than 1 γ per ml.	28 (57%)	24	4	85

TABLE 12

PROGNOSIS ACCORDING TO SENSITIVITY TO STREPTOMYCIN (BACTERICIDAL LEVEL) OF THE STRAINS ON FIRST ISOLATION

(for 55 cases)

CONCENTRATION OF STREPTOMYCIN PREVENTING GROWTH ON SUBCULTURES	NUMBER OF CASES	DEAD	ALIVE	MORTALITY
				per cent
Less than 10 γ per ml.	22 (40%)	9	13	40
More than 10 γ per ml.	33 (60%)	25	8	80

concentration of streptomycin for the subculture can be determined, and we designate it the *bactericidal level*. The value for this concentration is usually high. In table 12 the mortality rate according to this bactericidal level is shown.

Of 55 strains, 33 yielded subcultures in spite of one month's contact with more than 10 γ of streptomycin per ml. In the patients from whom these strains were obtained, the mortality rate (25 deaths of 33) was twice as high in the group with the 33 insusceptible strains as in the other group.

Late mortality: Aside from the over-all mortality, the time of death should be considered in order to appreciate the severity of a given symptom, for the factors causing late death could be different from those causing it early.

In table 13 is shown the influence of: (*1*) age, (*2*) state of consciousness, and (*3*) protein concentration in cerebrospinal fluid before treatment on both early (first

two months) and late mortality rate. It should be pointed out that it is the early mortality which varies between extremely wide limits (90 to 7 per cent) according to the state of consciousness of the child; the late mortality is very stable, approximately 20 per cent. In reality, however, the high incidence of early mortality in certain groups makes it misleading to compare in this way the incidence of late relapse in the different groups. The child has escaped from the main danger of the two first months. It is more accurate to evaluate the mortality rate in

TABLE 13

BEARING OF (a) AGE, (b) STATE OF CONSCIOUSNESS, (c) INITIAL PROTEIN CONCENTRATION IN CEREBROSPINAL FLUID, (d) REGIMEN OF TREATMENT ON BOTH EARLY (FIRST TWO MONTHS) AND LATE MORTALITY

	SURVIVAL	LATE MORTALITY	EARLY MORTALITY
Age			
	per cent	*per cent*	*per cent*
Under 1 year	25	19	56
1 to 6 years	42	21	37
6 to 21 years	63	20	17
State of Consciousness			
Coma	10	0	90
Stupor	34	22	44
Sleepiness	48	28	24
Drowsiness	67	17	16
Normal	73	20	7
Protein Concentration			
More than 150 mg. per 100 cc.	40	20	40
100 to 150 mg. per 100 cc.	52	20	28
Less than 150 mg. per 100 cc.	60	20	20
Regimens of Treatment			
I	26	27	47
II	35	52	13
III (See Table 14)	68	16	16
IV	57	7	36

the different groups (according to the general condition on admission) only in those patients who survived more than two months.

Thus, it appears that, if the over-all mortality rate is approximately 20 per cent, it varies somewhat in the different groups; and the more severe the general condition on admission, the greater the incidence of relapse.

Let us consider the group of children admitted with normal consciousness:

7 per cent died in the first two months.
20 per cent died later.
73 per cent survived.

This means in reality that, of 93 children who survived after two months, only 20 died later (21.5 per cent).

Let us consider now the children who were in *stupor* on admission:

44 per cent died in the two first months.
22 per cent died later.
34 per cent survived.

This means that, of 56 children who survived after two months, 22 died later (40 per cent).

It can be concluded that the general condition of the child on admission will decide the immediate prognosis and that it has some influence on the late mortality as well.

Regimens of treatment: Once we know the prognostic significance of this or that symptom, it becomes easier to determine the respective value of the different methods of treatment.

In table 14 (I, II, III, IV) are presented the four regimens that have been employed one after the other. In table 15 is shown the over-all mortality with the four different regimens.

It is clear that the early and late mortality rates have varied greatly in these four groups. In the first group there was a very high early mortality, partly explained by the late admission of the patients at the beginning of streptomycin therapy. In the second group, on the contrary, there was a very low early mortality but a very high percentage of late relapses. This second series is too short to be statistically significant. In the third group the results were much better, and in the fourth the mortality is again higher, but it should be noticed that, in reality, the late mortality is the lowest that we ever had. It is only the early mortality that increased, showing that it is either a bad series for an unexplained reason or a series in which patients were again admitted at a late stage of their meningitis. This is due, perhaps, to the fact that now all centers get streptomycin and only the bad cases are sent over to our clinic.

We have now adopted the following regimen: We give intrathecal treatment of streptomycin, *but not dihydrostreptomycin*, in a dose of 20 to 40 mg. per injection according to age and weight. Two such injections are given daily for the first ten days of therapy and one injection is given daily thereafter for approximately four months until the cerebrospinal fluid approaches normal. For an additional month one intrathecal injection is given every other day.

We give streptomycin by the intramuscular route, 250 mg. to 1 gm. daily, according to age and weight of the patient. The intramuscular streptomycin is discontinued only after the cerebrospinal fluid has been normal for two months. This means treatment for at least six or seven months, often longer. As a rule, we also administer para-aminosalicylic acid (PAS) (50 centigrams per kg. daily by mouth).

It is our belief that the main points of the treatment of tuberculous meningitis with streptomycin are now beyond discussion: general dosage, importance of

TABLE 14

REGIMENS OF TREATMENT

Regimen I: Streptomycin, 50 to 200 mg. per kg. daily by the intramuscular route
Streptomycin intrathecally, 50 to 100 mg. per kg. once daily

The average duration of treatment was four months. This represented a very high dosage both by intramuscular and intrathecal routes. Toxic accidents made rest periods necessary. Treatment was discontinued before cerebrospinal fluid was back to normal.

Regimen II: Streptomycin, 50 to 100 mg. per kg. daily by the intramuscular route
Streptomycin, 50 to 100 mg. per kg. intrathecally twice daily for a few days and once daily thereafter.
Average duration of treatment—five months

Intrathecal treatment with high dosage of streptomycin but of very short duration. Intramuscular treatment with lower dosage than in first regimen and with fewer rest periods, but discontinued before return to normal of cerebrospinal fluid and resumed only in case of relapse.

Regimen III Streptomycin, 50 mg. per kg. daily by the intramuscular route
Streptomycin, 25 to 50 mg. per kg. intrathecally daily at start and once daily thereafter with occasional rest periods.
Average duration of treatment—more than six months

Low dosage both intramuscularly and intrathecally. Continuous intramuscular treatment discontinued only after cerebrospinal fluid has been back to normal for two months. Long intrathecal treatment with rest periods.

Regimen IV: Streptomycin by intramuscular route as in *Regimen III*
Streptomycin by intrathecal route also as in *Regimen III*, but without any rest periods
Average duration of treatment—more than eight months

Intramuscular treatment as in *Regimen III*. Intrathecal treatment with no rest periods until cerebrospinal fluid is back to normal.

The general tendency has been to reduce the daily dosage of streptomycin (both intramuscular and intrathecal) and to increase the total duration of the treatment.

TABLE 15

STATISTICS ESTABLISHED ON FEBRUARY 1, 1950

REGIMENS OF TREATMENT*	NUMBER OF CASES	ALIVE	DEAD	MORTALITY	IN MORE THAN 2 MONTHS		IN LESS THAN 2 MONTHS	
					number	per cent	number	per cent
				per cent				
I	73	19	54	74	20	27	34	47
II	23	8	15	65	12	52	3	13
III	108	73	35	32	18	16	17	16
IV	58	33	25	43	4	7	21	36

*See Table 14.

intrathecal treatment, and treatment of long duration. Many points have not yet been established precisely, i.e., the best route of introduction for intrathecal treatment, the values and type of combined therapies, and the indications for neurosurgery.

These different methods of treatment carry different risks to the patient and they give very different results. It is of the greatest importance that we study the therapeutic results obtained thus far and take into consideration all of the other factors of good or bad prognosis. This only will teach us to choose the best treatment for each patient according to the severity of the disease. Such is our task.

GROWTH PATTERN AND VIRULENCE OF TUBERCLE BACILLI[1]

DIRAN YEGIAN AND JOSEPH KURUNG

(Received for publication October 17, 1951)

INTRODUCTION

The studies of Middlebrook and his associates (1, 2) have indicated a correlation between the morphologic growth characteristics of mammalian tubercle bacilli and their virulence. When cultured under specific conditions, the virulent strains formed "serpentine cords" in liquid medium and spreading colonies on agar medium, while attenuated strains presented cord patterns that were less oriented. On the other hand, avirulent variants of tubercle bacillus strains, cultivated under identical conditions, showed nonoriented clumping of the bacilli.

Any *in vitro* procedure which can define the degree of virulence is obviously of great importance for the study of tuberculosis, and every aid to the analysis of the problem should be employed. It is the purpose of this paper to describe a method for cultivating tubercle bacilli in a liquid medium in which cord formation is so marked that it permits better differentiation of the growth patterns of the highly virulent, attenuated, and avirulent strains.

MATERIALS AND METHODS

The following strains of mammalian tubercle bacilli were studied:

H37Rv, a highly virulent strain

Tubercle bacilli, several strains recently isolated from sputum in this laboratory

H37Ra, an avirulent variant of H37Rv

R1Ra, H4Ra, and JH16Ra, obtained recently from Trudeau Laboratory and reported to be avirulent for guinea pigs

R1Rv, a strain of low virulence for normal guinea pigs

Ravenel, a classical virulent bovine strain

BCG Albany, obtained from Dr. Konrad Birkhaug, labeled BCG 865 (series 2)

BCG, 3 strains obtained from Dr. René Dubos two years ago, labeled Tice, Phipps, and 317. The most virulent of these strains was reported to be 317.

Chromogenic acid-fast bacilli isolated from gastric washings, 8 strains.

All of these cultures were maintained by regular transfer in liquid medium (3) containing 0.05 per cent Tween and 0.5 per cent bovine albumin (Fraction V).

The degree of virulence of these strains was determined by intradermal and intraperitoneal injection of large numbers of bacilli in highly inbred, albino guinea pigs. The intradermal tests were observed until complete healing of the lesions. The animals were sacrificed on the thirty-fifth day after the intraperitoneal dose, and the results were based on the gross appearance of the tissues.

The medium employed for the demonstration of growth pattern was the same as that described above for maintenance of the stock cultures with the addition of 5 per cent of sterile human serum or plasma which had not been subjected to heat. Any modification of this medium will be mentioned in the

[1] From the Ray Brook State Tuberculosis Hospital, Ray Brook, New York.

discussion of the results. The inoculum was 0.1 ml. of an eight- to ten-day-old culture per 5 ml. of medium. A control culture without serum was inoculated similarly for comparison study. After ten to fifteen days of incubation the character of the growth was determined grossly by gentle shaking of the tubes and microscopically by the examination of the films stained by the Ziehl-Neelsen technique.

RESULTS

In this liquid medium containing human serum, the *Mycobacteria* studied showed three types of growth: flocculent, granular, and diffuse. The flocculent type of growth was produced by the virulent tubercle bacilli and diffuse growth by some of the avirulent chromogenic acid-fast microorganisms, the Phipps BCG strain, and some "reverse mutants" derived from a streptomycin-dependent variant isolated from the Albany BCG strain. Those strains of intermediate virulence showed granular growth, the granules ranging from fine to coarse. Although the gross appearance of the culture was found to be helpful, no differentiation of the degree of cord formation was possible on this basis alone; study of the stained film was necessary.

Stained preparations of highly virulent tubercle bacilli, including H37Rv (figure 1), strains recently isolated from sputum, and the Ravenel bovine strain (figure 7), were characterized by serpentine growth. The cords were long and winding or short and straight. The cells lay parallel to the long axis of the cord and were tightly packed (figure 6A). Occasionally a few bacilli got out of line and developed into a new cord branching from the original growth. The growth configuration of these strains was distinctive.

In those strains of tubercle bacilli which are completely devoid of virulence, H37Ra, H4Ra, JH16Ra, and R1Ra (figure 2), there was no tendency toward cord formation and the bacilli occurred in amorphous clumps.

The strains of intermediate virulence showed various degrees of cord formation but to a much less extent than the fully virulent strains (with one exception which will be discussed with the attenuated strains). The cords did not attain as great length, and many divided branches were seen which resembled the divisions of the finer branches of a tree (figure 6B). This is presumably due to the fact that the bacilli were only loosely adherent to each other and could readily get out of line to form many divisions instead of a long tortuous cord such as was formed by the virulent strains.

Strain R1Rv (figure 3) which was reported to have low virulence for guinea pigs showed a definite tendency toward cord formation, although the arrangement of the bacilli was loose and not well oriented. BCG, strain 317 (figure 8), the most virulent of the BCG cultures tested, showed more tightly packed cords than any other of the BCG strains. The Tice (figure 10) and Phipps (not shown) strains of BCG did not form cords while BCG, Albany strain (figure 9), which has slight virulence, formed loose cords similar to those of R1Rv. These findings were in accord with the *in vivo* virulence tests performed in the course of this study.

A culture of the avirulent strain H37Ra (H37Ra(x), figure 4), obtained

Fig. 1

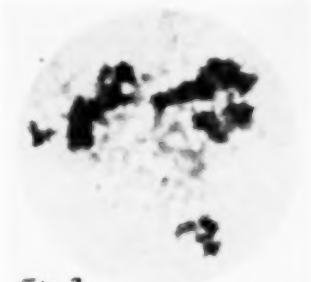


Fig. 2

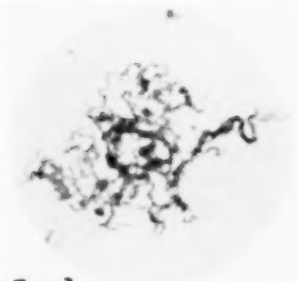


Fig. 3

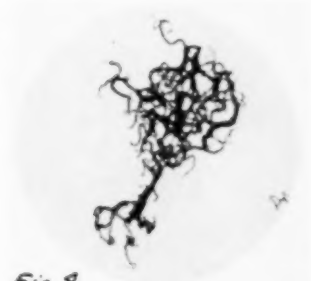


Fig. 4

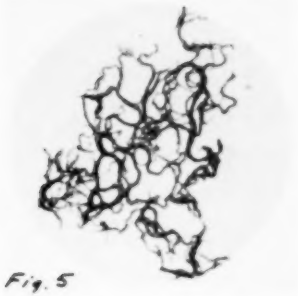


Fig. 5

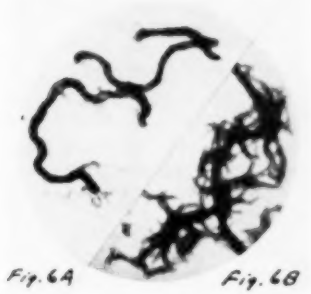


Fig. 6A Fig. 6B

FIG. 1. H37Rv, virulent human strain, showing characteristic serpentine growth. ×400.

FIG. 2. R1Ra, avirulent human strain, showing nonoriented clumping of bacilli. ×400.

FIG. 3. R1Rv, a strain of low virulence for normal guinea pigs, showing poorly oriented cord pattern with loose arrangement of bacilli. ×400.

FIG. 4. H36Ra(x), showing better cord formation than any attenuated strain studied. *In vivo* virulence tests confirmed this finding. ×400.

FIG. 5. Streptomycin-dependent variant from H37Rv, showing good formation although devoid of virulence. ×400.

FIG. 6A. Virulent strain, higher magnification, illustrating tightly packed cord with little tendency to branching. ×800.

FIG. 6B. Attentuated strain, higher magnification, showing less tightly packed cords with much branching. ×800.

several years ago from the Trudeau Laboratory and maintained during the past three years in the stock Tween-albumin medium mentioned previously, exhibited a cord pattern better than that shown by any of the attenuated strains. Because of this unexpected finding, a new culture of H37Ra was ob-

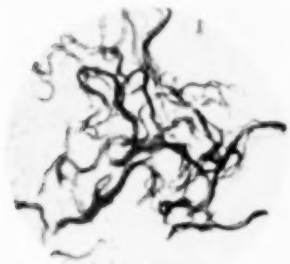


Fig. 7

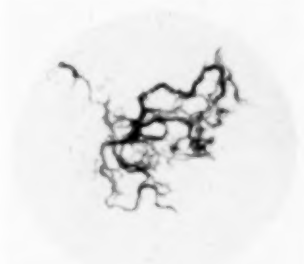


Fig. 8

Fig. 9

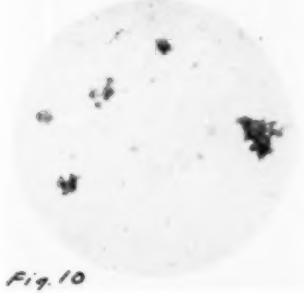


Fig. 10

FIG. 7. Ravenel, virulent bovine strain, showing cord formation characteristic of virulent tubercle bacilli. ×400.

FIG. 8. BCG 317, the most virulent of the BCG strains studied, showing better cord formation than the other BCG strains. ×400.

FIG. 9. BCG, Albany strain, of slight virulence, showing poorly oriented cord pattern similar to R1Rv. ×400.

FIG. 10. BCG, Tice, showing clumping of bacilli. This strain, like Phipps (not shown), showed no evidence of virulence by *in vivo* test. ×400.

tained from the same source, and when grown in liquid medium containing blood serum this strain did not form cords.

In vivo virulence studies in guinea pigs revealed decided gross lesions in the liver and spleen of the animal inoculated with the cord-forming culture (H37Ra(x)), while the recently obtained H37Ra strain gave rise to no visible abnormalities. Whether the change in the H37Ra(x) culture was due to spontaneous change in virulence (4) or to accidental factors, the virulence suggested

by the growth pattern was confirmed by the guinea pig response. Middlebrook has observed this phenomenon in his laboratory with strain H37Ra(5).

Probably the most interesting variant studied was a stable, streptomycin-dependent strain isolated from the virulent H37Rv. This culture, although incapable of producing any lesions in the guinea pig and apparently devoid of virulence (6), showed marked cord formation (figure 5) when cultivated in the medium used here. This was the only instance in which good cord formation was observed in an avirulent culture.

Eight strains of avirulent chromogenic *Mycobacteria* showed either diffuse or granular growth grossly and none showed any suggestion of cord formation when examined microscopically.

DISCUSSION

The present observations confirm the original observations of Middlebrook and Dubos that there is a relationship between the degree of cord formation and the virulence of mammalian tubercle bacilli. With the medium employed in the present study it is possible to correlate more closely the degree of cord formation with the virulence of attenuated strains.

Recent investigations by Suter and Dubos (7) have shown that to quantitate the degree of virulence or attenuation by morphologic growth pattern alone is not always reliable, at least in the case of certain variants of the BCG strains studied. These writers employed transparent agar medium (8) for the determination of colony pattern, classified as spreading, intermediate, and non-spreading. The present writers have found the results obtained on agar medium to be a less reliable index than those shown by the liquid medium used here.

The addition of a small amount of normal human blood serum or plasma to liquid Tween-albumin medium gives rise to marked serpentine growth of virulent tubercle bacilli. This effect was noted even when less than 1 per cent of serum was added, and normal sera from different animals proved to be as effective as human serum. This enhancement of cord formation can be explained in part by the observation of Davis and Dubos (9) that unheated serum or plasma has esterase activity for Tween 80, splitting the oleic acid from the rest of the molecule and thereby destroying the surface active effect of Tween on tubercle bacilli.

Only one of the many strains of mammalian tubercle bacilli studied failed to show agreement between growth pattern and virulence. This strain, a streptomycin-dependent variant derived from the parent virulent strain H37Rv, proved to be a good cord-former although it is not virulent for guinea-pigs even when the animals are treated with streptomycin. This exception, however, does not disprove the point made by Middlebrook and Dubos that the growth pattern of tubercle bacilli gives an indication of the degree of virulence. It would indeed be rare if any single factor could account for all the components of virulence. In general, it may be said that, while all cord-formers are not necessarily virulent, all virulent strains are cord-formers.

SUMMARY

The addition of normal blood serum or plasma to liquid Tween-albumin medium favors formation of cords by virulent strains of tubercle bacilli.

In this medium the degree of cord formation has been found to correspond with the *in vivo* findings with regard to virulence. The only exception among the strains tested occurred with a streptomycin-dependent variant of strain H37Rv which, although avirulent, showed good cord formation.

SUMARIO

El Patrón del Crecimiento y la Virulencia de los Bacilos Tuberculosos

La adición de suero o plasma sanguíneo normal al medio líquido de Tween-albúmina hace que los bacilos tuberculosos virulentos crezcan en cordones serpentinos.

Obsérvase que, en dicho medio, la intensidad de la formación de cordones correspondía a los hallazgos *in vivo* con respecto a virulencia. La única excepción en las cepas comprobadas fué una variante estreptomicinófila de la cepa H37RV, la cual, aunque virulenta, mostró buena formación de cordones.

RESUME

Type de croissance et virulence du bacille tuberculeux

L'addition de sérum sanguin normal ou de plasma au milieu liquide Tween-albumine donne, avec les bacilles tuberculeux virulents, des colonies en cordons sinueux.

Dans ce milieu, il a été observé que le degré de formation en cordon correspondait au degré de virulence *in vivo*. La seule exception, parmi les souches expérimentées, s'est produite avec une variante streptomycino-sensible de la souche H 37 Rv qui, bien que virulente, a donné une bonne formation en cordon.

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USE OF OXIDATION-REDUCTION DYES IN THE DETERMINATION OF VIRULENCE OF MYCOBACTERIA IN VITRO[1]

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INTRODUCTION

A simple, differential, *in vitro* test for virulence of *Mycobacteria* has long been sought as an adjunct to cultural techniques in the laboratory diagnosis of tuberculosis. Several investigators have reported on oxidation-reduction potential factors which have been used to determine virulence of *Mycobacteria*. Aksianzew (1), in 1933, using the standard Thunberg technique, reported that virulent *Mycobacterium tuberculosis* (var. *hominis*) decolorized methylene blue more rapidly than did BCG. Roulet, Sydler, and Zeller (2), in 1946, studying the enzymatic degradation of certain oxyacids by *Mycobacteria*, observed incidentally that *Mycobacterium smegmatis* decolorized methylene blue at a more rapid rate than did *M. tuberculosis* (var. *hominis*).

Bloch (3) recently reported that methylene blue was reduced by acid-fast saprophytes in one to three minutes and by avirulent tubercle bacilli in two to fifteen minutes, whereas young virulent strains did not reduce the dye within sixty minutes. This technique has the disadvantages that only cultures in Tween-albumin liquid medium can be used, that the time of reduction of the strains overlaps, and that pathogenic, viable organisms must be handled repeatedly.

Since little work has been reported on the oxidation-reduction potentials of *Mycobacteria*, it was thought of interest to reinvestigate the phenomenon. The purpose of this study was twofold: first, to determine if virulent and avirulent strains of *Mycobacteria* exhibit different oxidation-reduction potentials; and, second, if consistent differences are noted, to adapt the results to a simple dye test.

MATERIALS AND METHODS

The following stock strains of *Mycobacteria* were used as test organisms in the preliminary potentiometric and colorimetric studies: human (H37Rv), avian (Kirchberg), bovine (Ravenel), 7 acid-fast saprophytes, 4 strains of BCG, and one strain of attenuated human (H37Ra). Potentiometric studies were also made with 4 "wild" strains of human-type *M. tuberculosis* and 3 "wild" acid-fast saprophytes recently isolated from pathologic material.

The 15 stock cultures were checked for viability by subculturing and, for virulence, by inoculation into appropriate animals. Thus, human strains were inoculated into guinea pigs, bovine strains into rabbits, and avian strains into chickens. The human, avian, and bovine strains produced typical tuberculous lesions in susceptible animals. The BCG, H37Ra, and saprophytic acid-fast strains were avirulent. All cultures were further examined for con-

[1] From the Communicable Disease Center, Public Health Service, Federal Security Agency, Chamblee, Georgia.

taminants by microscopic examination of stained smears and by subcultures on nutrient agar. All cultures which were proved or suspected to contain contaminants were discarded.

In order to measure oxidation reduction potentials of these organisms in a uniform medium, 0.1 ml. (0.1 mg.) of a homogenous suspension (4) of each of the 22 strains was inoculated into 125 ml. of Youmans' modification (5) of Proskauer and Beck medium without plasma or serum. Ordinary cotton plugs were used. These suspensions were held at 37° C. Potentiometric readings were made of the suspensions after 120 hours at 37° C. and daily thereafter for a period of 20 days on a Beckman Model G pH meter adapted to determine oxidation reduction potentials. Calomel and platinum electrodes were used throughout the study. The platinum electrode was washed in hot chromic acid prior to use. Potentiometric readings (in volts) were made on 3 ml. of suspension which were withdrawn aseptically with a pipette and placed in a 5 ml. sample cup. The contaminated sample cups were discarded into a can containing phenol and were autoclaved. Control readings were made on 3 ml. of incubated, uninoculated medium at daily intervals in parallel with the test cultures, and the results were subtracted from the readings of the inoculated medium.

RESULTS

All virulent strains of *Mycobacteria* tested (with the exception of avian) presented almost identical oxidation-reduction curves throughout the growth period. The attenuated human (H37Ra) and BCG strains presented curves different from those produced by the virulent or avirulent strains. The avian strain presented a curve which seemed to be characteristic of avian-type *Mycobacteria*. The avirulent strains produced curves which were distinctly different from those of the virulent or attenuated strains. Typical curves for virulent, avirulent, and attenuated strains of *Mycobacteria* are shown in figure 1.

These determinations indicated that redox dyes having an E_o' potential of approximately -0.2 volts would be decolorized by avirulent strains but would not be affected by virulent strains of *Mycobacteria*. The following four oxidation-reduction dyes were therefore selected for use in the dye decolorization test: phenol indophenol (E_o' potential in volts -0.227 at pH 7.0)[3]; sodium benzenone-indophenol (E_o' potential in volts -0.228 at pH 7.0)[3]; sodium benzenoneindo-3′-chlorophenol (E_o' potential -0.225 at pH 7.0)[3]; and sodium-2,6-dibromo-benzenone-indophenol (E_o' potential in volts -0.221 at pH 6.93)[3]. These four dyes were used for extensive trials in the differentiation of virulent from avirulent *Mycobacteria*.

Since each of the dyes possesses a different degree of solubility, stock solutions of the four dyes were prepared by dissolving them in phosphate buffer solution, pH 7.0 (5.99 gm. NaH_2PO_4 + 7.098 gm. Na_2HPO_4, diluted to one liter), as follows:

1) Phenol indophenol: 5 mg. dissolved in 10 ml. of buffer solution
2) Sodium benzenoneindophenol: 5 mg. dissolved in 5 ml. of buffer solution
3) Sodium benzenoneindo-3′ chlorophenol: 5 mg. dissolved in 25 ml. of buffer solution
4) Sodium 2,6 dibromobenzenone indophenol: 5 mg. dissolved in 25 ml. of buffer solution.

Gentle heat was required to dissolve dyes numbers 2 and 3. These solutions

[3] LaMotte Chemical Products Company, Baltimore, Maryland.
[3] Eastman Kodak Company, Rochester, New York.

were stored in a cool, dark place and were considered suitable for use as long as no change in color was noted. Immediately before use, dilutions were made as follows from the stock solutions to prepare the dyes for use in the test:

1) Phenol indophenol: 1 ml. diluted with 5 ml. of buffer solution
2) Sodium benzenoneindophenol: 1 ml. diluted with 3 ml. of buffer solution
3) Sodium benzenoneindo 3′ chlorophenol: 3 ml. diluted with 2 ml. of buffer solution
4) Sodium 2,6-dibromobenzenone-indophenol: 2 ml. diluted with 15 ml. of buffer solution.

Control tests with known organisms were set up as follows: 0.15 ml. portions of the four dyes were placed in three rows of four depressions of a white, porcelain, color-reaction spot plate. To the first row of depressions nothing was added.

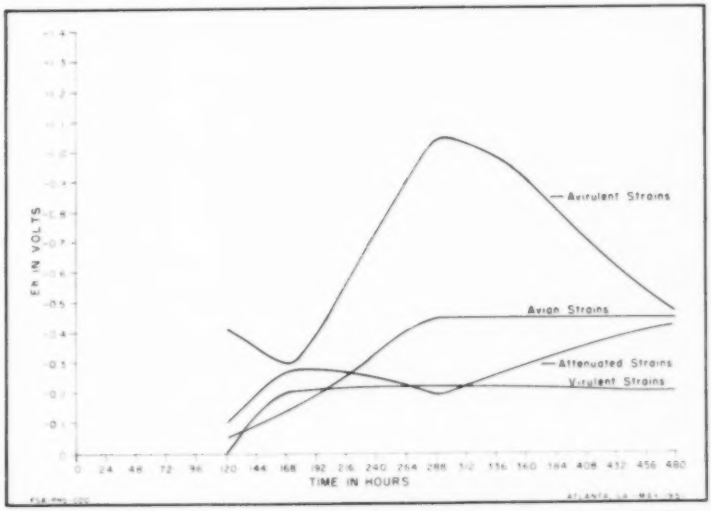

FIG. 1. Oxidation-reduction potentials of various strains of acid-fast bacilli.

To each of the four depressions of the next row were added approximately 5 mg. of the avirulent saprophyte *Mycobacterium phlei* scraped from a slant of Löwenstein medium (6). (The amount of organisms to be used for each test was approximated by taking a heaping spadeful of growth on a platinum spade 2 mm. wide by 5 to 7 mm. long.) The same amount of the virulent H37Rv strain of *M. tuberculosis* (var. *hominis*) was added to the last row. The suspensions were mixed thoroughly by means of a wooden applicator which was discarded immediately into a can containing phenol. The controls were allowed to stand fifteen minutes with occasional rotation.

Within this time limit, the four dyes containing the avirulent saprophyte (*M. phlei*) were completely decolorized. The dyes containing the suspensions of

virulent organisms retained some color. In some cases, further dilution of dyes was necessary in order to show these differences.

Determinations were then made on the 15 stock strains of acid-fast bacilli of known virulence or avirulence, using the method described in the preceding paragraph. The results were read by comparison with "known organism" and color controls. Organisms producing complete decolorization of all four dyes were recorded as nonvirulent. These notations are used in tables 1 and 2. Tests in which the controls (known organisms or dyes) gave unsatisfactory results were discarded.

TABLE 1

RESULTS OF TESTS FOR DECOLORIZATION OF DYES BY STOCK STRAINS OF MYCOBACTERIA

STRAIN OF MYCOBACTERIUM	DYE REACTION	ANIMAL PATHOGENICITY
Human (H37Rv)	Virulent*	Positive
Attenuated human (H37Ra)	Virulent	Negative
Attenuated human (R_1)	Nonvirulent†	Low virulence
Bovine (2 strains)	Virulent	Positive
BCG (4 strains)	Virulent	Negative
Avian (Kirchberg)	Nonvirulent	Positive
Acid-fast saprophytes (5 strains)	Nonvirulent	Negative

* Failed to decolorize.
† Decolorized.

TABLE 2

RESULTS OF TESTS FOR DECOLORIZATION OF DYES BY "WILD" STRAINS OF MYCOBACTERIA

NUMBER OF SPECIMENS	TYPE OF MYCOBACTERIUM	INITIAL DYE REACTION	GUINEA PIG	FINAL DYE REACTION
230	*M. tuberculosis* (*hominis*)	Virulent*	Positive	Virulent
7	*M. tuberculosis* (*hominis*)	Nonvirulent†	Positive	Virulent
34	Saprophytes (acid-fast)	Nonvirulent	Negative	Nonvirulent

* Failed to decolorize.
† Decolorized.

The dye decolorization reaction was then used to test 237 "wild" strains of human-type *M. tuberculosis* and 34 "wild" strains of acid-fast saprophytes (all identified by cultural characteristics) isolated from routine pathologic material. All of the "wild" strains of *M. tuberculosis* used in the dye test produced typical, extensive, pathologic lesions in guinea pigs. Pathologic material from infected organs was recultured onto Löwenstein medium, and six weeks later the cultures were again tested with the dyes. None of the "wild" saprophytes produced any evidence of pathologic lesions and hence were not recovered from animals for retesting.

All of the stock avirulent cultures except H37Ra and the various BCG strains

decolorized the four dyes completely in fifteen minutes. The R_1 strain (low virulence) and the avian strain (virulent) also decolorized the dyes completely. However, the remainder of the stock virulent cultures either did not decolorize any of the dyes or decolorized only one or two dyes slightly. These data are shown in table 1. As noted above, the H37Ra strain and the BCG strains, both of attenuated virulence, gave reactions indicating virulence.

DISCUSSION

As shown in table 1, the H37Ra strain and the BCG strains reacted in the dye test as virulent strains of *Mycobacteria*. A possible explanation for this finding suggests itself if it be postulated that the oxidation-reduction dyes used in the study are reduced (decolorized) through the action of certain dehydrogenase systems, the redox potentials of which have been calculated to be in the range -0.28 to -0.29 volts (7). The findings reported above would seem to indicate that in typically virulent strains of *Mycobacteria* these specific dehydrogenases are lacking. Moreover, in avirulent strains (BCG, H37Ra) which have been derived from virulent organisms, it is probable that they would also be absent. These theoretical observations would suggest that the dye test depends primarily upon the presence of certain enzyme systems which appear to be associated with avirulence.

It will be seen in table 2 that 230 of 237 specimens of "wild" virulent *M. tuberculosis* (var. *hominis*), as identified by cultural characteristics, failed to decolorize the dyes both before and after passage through guinea pigs. With these 230 specimens then, as well as with the 34 acid-fast saprophytes, there was complete agreement between cultural characteristics, animal pathogenicity, and dye reaction. Seven of the strains of human-type tubercle bacilli which originally decolorized the dyes failed to do so following animal passage.

The difference in dye reaction of 7 of the specimens before and after animal passage is difficult to explain. When the specimens were subcultured on nutrient agar, acid-fast bacteria appeared in one to three days. Therefore, it was assumed that these 7 cultures had contained saprophytic *Mycobacteria* not easily discernible on first isolation from pathologic material. These mixed cultures could have decolorized the dyes and thus have yielded the 7 negative, *in vitro*, virulence tests. Passage of these cultures through animals resulted in the recovery of pure cultures of virulent human tubercle bacilli. These would not decolorize the dyes, thus producing a positive *in vitro* virulence test. Although it is not supported by adequate experimental evidence, the possibility exists that some of the "wild" strains of *M. tuberculosis* (var. *hominis*), having become attenuated on culture, recovered their virulence more fully on passage through animals.

To obtain the best results with this test, several precautionary measures are necessary:

(a) Typical isolated colonies should be selected for use in the spot plates in order to minimize chance of false results. (b) Five to 10 mg. of culture should be used; less than 5 mg. of saprophytes may yield false positive reactions; more than 10 mg. of virulent *Mycobacteria* may cause moderate decolorization of the dye in the allotted time and make

the interpretation difficult. (c) All cultures should be viable. Dead cultures, whether virulent or avirulent, will not decolorize the dyes. (d) Strains of known avirulent and virulent *Mycobacteria* should be tested as controls before the test is made on unknown cultures. (e) Even though the reactions of the four dyes are usually the same, it is better to continue using all four dyes rather than one or two dyes in order to equalize the variations in size of inoculum. (f) Since this procedure involves the manipulation of pathogenic material, it is particularly necessary to use safety measures. The tests should be performed under a safety hood. The spot plates should be sterilized immediately after use.

In its present form this test cannot be used routinely as an *in vitro* virulence test to replace animal inoculations because of the false reactions noted. However, it might possibly be used as a confirmatory test in those instances in which the results of the tests are in complete agreement with the cultural characteristics of the various *Mycobacteria*. In any case, it should be noted that virulent human tubercle bacilli containing contaminants may or may not give the typical reaction of virulence with the dyes, whereas typical cultures of saprophytic *Mycobacteria* with a small number of viable organisms may or may not give the typical reaction of avirulence. Perhaps other *in vitro* virulence tests in conjunction with this test and observation of cultural characteristics may serve to eliminate animal inoculations in many instances.

It is not recommended that this test be adopted, either singly or in combination, for routine use in a diagnostic laboratory until such time as its value has been determined by other laboratory workers. An evaluation of this test is in progress, using routine pathologic cultures. Comparison of the data obtained thus far in comparison with animal results indicates that the oxidation-reduction dye reaction is of value as an aid in the laboratory diagnosis of tuberculosis.

SUMMARY

A spot-plate virulence test utilizing organisms from a solid medium suspended in solution of oxidation-reduction dyes has been described.

Nonviable or contaminated cultures give false results.

The *in vitro* test described may be used in conjunction with cultural characteristics to eliminate animal inoculations in many instances.

There is need for further investigation of this test before it is adopted for routine use.

SUMARIO

Empleo de los Colorantes Oxido-Reductores en la Determinación de la Virulencia de Mycobacteria in Vitro

La prueba instantánea en placa de la virulencia *in vitro* aquí descrita utiliza microbios obtenidos de un medio sólido suspendido en solución de colorantes oxido-reductores.

Los cultivos no viables o contaminados dan resultados falsos.

La prueba *in vitro* descrita puede ser usada, junto con las características culturales, para eliminar en muchos casos las inoculaciones en animales.

Necesítanse más investigaciones de esta prueba antes de adoptarla para empleo corriente.

RESUME

Utilisation de colorants ayant des propriétés oxydo-réductrices pour la détermination de la virulence des mycobacteria in vitro

Description du test de virulence "spot plate" (sur lame) en utilisant des bactéries provenant d'un milieu solide, suspendu dans une solution de colorants oxydo-réducteurs.

Les cultures non viables ou contaminées donnent des résultats faux.

Le test *in vitro* décrit peut être utilisé en conjonction avec les méthodes de culture caractéristiques pour éliminer, dans un certain nombre de cas, l'inoculation à l'animal.

Une étude plus complète de ce test est nécessaire, avant de l'adopter d'une manière habituelle.

Acknowledgment

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A COMPARATIVE STUDY OF THE HEMAGGLUTINATION TEST FOR ANTIBODIES AND ITS HEMOLYTIC MODIFICATION IN TUBERCULOSIS[1]

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INTRODUCTION

In 1948, Middlebrook and Dubos (1) described a specific hemagglutination test which employs the use of washed sheep erythrocytes sensitized with aqueous extracts of tubercle bacilli. These sensitized erythrocytes are rendered agglutinable by specific antibodies in the sera of experimental tuberculous animals and tuberculous patients. Smith and Scott (2, 3) substituted a special Old Tuberculin, 4 times the standard strength, for the aqueous extract. Observations on this reaction were reported by Rothbard, Dooneief, and Hite (4). In 1950, Middlebrook (5) reported a modification of this test wherein complement is added to the reaction system, thereby making it a test of hemolysis rather than one of hemagglutination. The present paper is concerned with a comparison study of the hemagglutination test and its hemolytic modification, with sera from known tuberculous patients and from those known not to have tuberculosis.

MATERIALS AND METHODS

The positive sera were obtained from patients at Triboro Hospital with roentgenographic evidence of pulmonary tuberculosis plus the demonstration of *M. tuberculosis* in the sputum. The negative sera were obtained from the laboratory staff and from Blood Bank donors.

The sera to be tested were collected as for a Wassermann test. They were kept in the cold or, if held for a length of time, they were stored in the deep freeze at $-10°C$. The sheep erythrocytes were obtained in Alsever's solution from the Certified Blood Donor Agency.

The preparation of the materials and the technique of the hemagglutination reaction were exactly as described by Middlebrook and Dubos (1) with the exception of the following modifications:

(a) Instead of the polysaccharide extract of the tubercle bacilli, the antigen used for the sensitization of sheep erythrocytes consisted of Lederle's "Special Tuberculin",[2] 4 times standard strength, which was diluted with eleven volumes of phosphate buffered saline, as described by Scott and Smith (2). (b) In the absorption of the serum with untreated sheep erythrocytes to remove antibodies unrelated to tuberculous infection, it was found that a single absorption of 2 ml. of 1:2 dilution of inactivated serum with 0.3 ml. packed, washed, untreated sheep erythrocytes, allowed to stand at room tem-

[1] From the Department of Bacteriology, Triboro and Queens General Hospitals, Jamaica, New York.

[2] Kindly supplied to us by Dr. Piersma of Lederle Laboratories, Pearl River, New York.

perature for fifteen minutes, was sufficient. A second absorption was necessary in only 12 instances, that is, when the erythrocyte control tube, containing unsensitized cells and absorbed sera, showed hemagglutination. (c) A 0.3 per cent suspension of sheep erythrocytes was used in the hemagglutination test instead of the 0.2 per cent suspension, and the test was read with the aid of a microscope mirror.

The hemolytic modification of the hemagglutination test was performed exactly the same way and with the same materials as those used in the hemagglutination test, except that an excess of "absorbed complement" was added to each tube. The "absorbed complement" was prepared in the manner described by Middlebrook (5). In the first half of the study, the complement was absorbed at room temperature (25°C.). After the publica-

TABLE 1

RANGE OF HEMAGGLUTININ AND HEMOLYTIC TITERS FOUND WITH 100 KNOWN TUBERCULOUS CASES AND 88 KNOWN NONTUBERCULOUS CASES

TITER	TUBERCULOUS CASES		NONTUBERCULOUS CASES			
	Agglutinin	Hemolytic	Agglutinin		Hemolytic	
	Number	Number	Number	Per cent	Number	Per cent
0	3	27	18	20	79	90
1:2	8	3	21	24	2	2
1:4	20	5	23	26	4	4
1:8	17	18	21	24	2	2
1:16	28	6	2	2	1	1
1:32	9	14	3	3	—	—
1:64	8	15	—	—	—	—
1:128	5	6	—	—	—	—
1:256	2	2	—	—	—	—
1:512	—	3	—	—	—	—
1:1,024	—	1	—	—	—	—
Total....	100	100	88		88	

— = none.

tion of the details of the procedure by Middlebrook (6), the remainder of the hemolytic tests were performed by absorbing complement at 4°C. Forty-eight of the original group, wherein the procedure was carried out at room temperature throughout, were repeated, now absorbing complement at 4°C. The results were identical in all instances.

In each series of tests, the hemagglutination as well as the hemolytic modification, was included a known positive standard rabbit serum prepared by intravenous injection of heat-killed bovine tubercle bacilli (Ravenel)[3] as described by Rothbard and associates (4).

During the early part of the experience with the hemolytic tests, one rack of tests failed to be discarded after the results had been recorded. The rack remained standing at room temperature. The following morning it was noticed

[3] Obtained through the courtesy of Mr. William Steenken, Jr., Trudeau Sanatorium, Trudeau, New York.

TABLE 2

COMPARISON OF HEMAGGLUTININ AND CORRESPONDING HEMOLYTIC TITERS FOUND IN 100 KNOWN TUBERCULOUS CASES

HEMOLYTIC TITER	AGGLUTININ TITER	NUMBER OF CASES
0	0	2
1:8	0	1
0	1:2	7
1:32	1:2	1
0	1:4	6
1:2	1:4	3
1:4	1:4	2
1:8	1:4	4
1:16	1:4	2
1:32	1:4	1
1:64	1:4	2
0	1:8	7
1:4	1:8	2
1:8	1:8	2
1:16	1:8	2
1:32	1:8	2
1:64	1:8	2
0	1:16	3
1:4	1:16	1
1:8	1:16	7
1:16	1:16	2
1:32	1:16	8
1:64	1:16	3
1:128	1:16	3
1:1,024	1:16	1
0	1:32	1
1:8	1:32	2
1:64	1:32	2
1:128	1:32	1
1:256	1:32	1
1:512	1:32	2
0	1:64	1
1:8	1:64	1
1:32	1:64	2
1:64	1:64	3
1:512	1:64	1
1:8	1:128	1
1:64	1:128	3
1:256	1:128	1
1:128	1:256	2
Total cases		100
Total number with identical titers		11

that the tests which had shown no hemolysis the day before now showed agglutination of erythrocytes, usually to the same titer as did the hemagglutination test of the same sera. Since that observation, all of the negative hemolytic

tests have been kept at room temperature, overnight, after they have been interpreted at the end of one hour at 37°C. in the waterbath.

RESULTS

The tuberculous sera were all obtained from patients with roentgenographic evidence of pulmonary tuberculosis plus the demonstration of *M. tuberculosis* in sputum. The nontuberculous sera were obtained from persons of the laboratory staff who had negative roentgenograms and who reacted cutaneously to Old Tuberculin, and also from Blood Bank donors who were in apparent good health, who had negative Wassermann tests, but on whom no chest roentgenograms or tuberculin tests were done.

TABLE 3

COMPARISON OF HEMAGGLUTININ AND CORRESPONDING HEMOLYTIC TITERS FOUND IN 88 KNOWN NONTUBERCULOUS CASES

HEMOLYTIC TITER	AGGLUTININ TITER	NUMBER OF CASES
0	0	18
0	1:2	19
1:4	1:2	1
1:16	1:2	1
0	1:4	21
1:2	1:4	1
1:4	1:4	1
0	1:8	17
1:2	1:8	1
1:4	1:8	2
1:8	1:8	1
0	1:16	2
0	1:32	2
1:8	1:32	1
Total cases		88
Total number with identical titers		20

Table 1 shows the range of agglutinin and hemolytic titers in the 100 tuberculous and 88 nontuberculous cases. Among the tuberculous cases, 31 per cent of the hemagglutination tests and 35 per cent of the hemolytic tests showed a titer of 1:4 or less. Among the nontuberculous cases, 70 per cent showed an agglutinin titer and 96 per cent showed a hemolytic titer of 1:4 or less (above first upper dotted line in table 1). It can also be seen from table 1, that the tuberculous cases show agglutinin titers ranging from 0 to 1:256 and hemolytic titers from 0 to 1:1,024; whereas with the nontuberculous sera, the hemagglutinin titers range from 0 to 1:32 and the hemolytic titers from 0 to 1:16 (second lower dotted line table 1). It seems significant that among the nontuberculous cases, 20 per cent were completely negative by hemagglutination but, in contrast, 90 per cent by hemolytic test. Moreover, it seems significant that the hemolytic tests show a higher range of titers among the tuberculous

cases than do the hemagglutination tests and a lower range among the nontuberculous cases.

The hemolytic test appears to be more specific than the hemagglutination test but, as yet, not sufficiently, selectively, sensitive. If 1:8 were considered a significant titer, as suggested by Thalhimer (7), then the hemolytic test would

TABLE 4

COMPARISON OF TITERS FOUND IN ORIGINAL HEMAGGLUTINATION TESTS AND THE HEMAGGLUTINATION FOUND AFTER ALLOWING NEGATIVE HEMOLYTIC TESTS TO STAND AT ROOM TEMPERATURE OVERNIGHT

ROUTINE HEMAGGLUTINATION TEST	ROUTINE HEMOLYTIC TEST	OVERNIGHT HEMOLYTIC TEST	NUMBER OF CASES		
Agglutinin (1) Titer	Hemagglutinin Titer	Agglutinin (2) Titer			
0	0	0	5		
1:2	0	1:2	2	Identical	24
1:4	0	1:4	11		
1:8	0	1:8	6		
0	0	1:2	1		
1:2	0	0	1		
1:2	0	1:4	3		
1:4	0	1:2	1	Twofold difference	16
1:4	0	1:8	1		
1:8	0	1:4	7		
1:16	0	1:8	2		
1:8	0	1:4 Hemolyzed above 1:4	1	Hemolyzed	2
1:64	0	1:8 Hemolyzed above 1:8	1		
0	0	1:8	1		
1:2	0	1:8	1	More than twofold	
1:4	0	1:16	1	difference	4
1:8	0	1:2	1		
Total			46		

appear to be more specific, for, as illustrated in table 1, 35 per cent of the tuberculous cases and 96 per cent of the nontuberculous cases show titers of 1:4 or less in the hemolytic tests, as compared with 31 per cent of the tuberculous and 70 per cent of the nontuberculous cases which show these same titers in the hemagglutination tests.

Tables 2 and 3 illustrate the lack of correlation between the two tests. Only 11 of 100 tuberculous cases and 20 of the 88 known nontuberculous cases showed identical titers. Among the tuberculous cases, 2 were identically negative in

both the hemagglutination and hemolytic tests, 2 in 1:4 dilution, 2 in 1:8, 2 in 1:16, and 3 cases in 1:64 dilution. Among the nontuberculous cases, 18 were negative in both tests, one case in 1:4, and one in 1:8 dilution. It is of interest, however, that the cases showing higher agglutinin titers also show more of the higher hemolytic titers. As illustrated in table 2, sera with negative hemagglutination titers show hemolytic titers up to 1:8; among those with hemagglutinin titers of 1:2, one serum had a hemolytic titer of 1:32; and, among those cases with hemagglutinin titers ranging from 1:4 to 1:256, the maximum hemolytic titers ranged from 1:64 to 1:1,024.

It was found that negative hemolytic tests of sera with positive hemagglutinin titers, on standing at room temperature overnight, would show the hemagglutination, usually to the same titer or within a twofold difference. Frequently, however, after overnight standing, the negative hemolytic tests were found to be hemolyzed in some or all of the tubes and therefore could not be checked for correlated agglutinin titers. In table 4 is listed a comparison of the hemagglutinin titers of 46 sera, i.e., a comparison of the agglutinin titers found in the original hemagglutination tests (column 1, Agglutinin 1) with those found in the instances in which the negative hemolytic tests were allowed to stand at room temperature overnight (column 3, Agglutinin 2). Twenty-four showed identical hemagglutinin titers, 16 showed a twofold difference in either direction, 2 were hemolyzed and therefore could not be checked for agglutinin titer, and 4 showed more than a twofold difference.

As Middlebrook suggested, the reactions in the two tests may be due to differences in the antigen or antibody involved in the agglutination and in the lysis of sensitized erythrocytes.

SUMMARY

A comparison study shows that the hemagglutination test and its hemolytic modification for the detection of antibodies in tuberculosis do not show good correlation. It is suggested that the antibodies which are measured in the two tests are different.

It appears that the hemolytic modification is the more promising test as a possible diagnostic tool for case finding. Both tests should be explored from the standpoint of follow-up in cases of known active tuberculosis.

SUMARIO

Estudio Comparado de la Hemaglutinorreacción y de la Modificación Hemolítica de la Misma en la Tuberculosis

Un estudio comparado revela que la prueba de la hemaglutinación para la tuberculosis y la modificación hemolítica de la misma no muestran buena correlación. Indícase que los anticuerpos medidos en las dos pruebas son distintos.

Parece que la modificación hemolítica es la prueba que promete más como posible instrumento diagnóstico para el descubrimiento de casos. Ambas pruebas deben ser exploradas desde el punto de vista de la observación subsiguiente de casos activos conocidos.

RESUME

Etude comparative du test d'hémagglutination et des modifications de l'hémolyse dans la tuberculose

Une étude comparative montre qu'il n'existe pas une bonne corrélation entre le test d'hémagglutination pour le diagnostic de la tuberculose et sa modification hémolytique. Les auteurs suggèrent que les anticorps qui sont mesurés dans ces deux tests sont différents.

Il semble que la modification hémolytique soit le test qui offre le plus de promesses comme instrument de diagnostic utilisable pour déceler les cas de tuberculose. Les deux tests devront être explorés du point de vue de la mise en observation des cas en activité identifiés.

Acknowledgment

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EFFECTS OF SIMULTANEOUS SKIN TESTS ON SIZE OF TUBERCULIN REACTIONS[1,2]

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INTRODUCTION

It has been stated (1) that when several simultaneous skin tests are made on a single animal the reaction sizes may be appreciably altered. Since the validity of potency determinations obtained in this way could be questioned, the writers undertook a study comparing reactions to three substances when they were tested at the same time (multiple testing) with those obtained when each substance was tested alone (single testing) on the same animals.

MATERIALS

Three test substances were used. One of these was PPD-S (2), a purified whole protein fraction isolated from heated tuberculin, which has served as a standard for use in skin testing. Two other protein fractions recently isolated from unheated tuberculin filtrates were chosen for the other test substances, since they had proved to differ in their biological potencies (3) as well as in their chemical compositions (4, 5). An A-type protein fraction designated A 4 (6) was much more potent, and the C protein much less potent, than the PPD-S. This result is confirmed in this study. All tests were given intradermally in a dose of 0.0025 mg. per 0.1 ml., based on micro-kjeldahl nitrogen determinations.

PLAN OF INVESTIGATION

Twenty guinea pigs, previously infected with a moderately virulent strain (DT) of human-type tubercle bacillus, were selected for the experiment on the basis of strong reactions to PPD-S in past skin tests. These were divided arbitrarily into four groups of five animals each. *Groups 1*, *2*, and *3* each received a single test with a different substance in each of the first three weeks. A latin-square arrangement was used to eliminate the main effects of differences in response in different weeks and groups of animals from the average effects due to the use of different substances. The animals in *Group 4* were given the three substances simultaneously once each week for three weeks.

If the design shown in table 1 could have been completed, *Groups 1*, *2* and *3* would have been multiply tested in each of the next three weeks, and *Group 4* would have been singly tested with each substance in successive weeks. Unfortunately, it was not possible for the original investigator to continue the experiment after the third week and another experimenter did the testing and observations during the fourth week when the experiment was terminated.

Six sites of injection were utilized, three on each side of the animal. Multiply

[1] From The Henry Phipps Institute, University of Pennsylvania, and the Philadelphia Tuberculosis and Health Association, Philadelphia, Pennsylvania.

[2] Aided by assistance from the Tuberculosis Control Division of the Public Health Service and by a grant from the Committee on Medical Research of the American Trudeau Society, medical section of the National Tuberculosis Association.

tested animals received three injections, two on one side and one on the other. Although the sites were varied from week to week they were not randomized, and differences between sites are not considered in the analysis. As the sites were kept within a small area, it is believed that this does not constitute a serious disadvantage.

In each week of the experiment, several animals without known infection were tested with all three substances in order to make sure that they were eliciting nothing but specific reactions. In most instances none or only trace reactions were observed.

TABLE 1

SCHEDULE FOR TESTING OF DIFFERENT GROUPS OF GUINEA PIGS

DATE TESTED 1950	GROUPS TESTED WITH PRODUCTS			
	PPD-S	A 4	C	All Three Fractions
First week May (9-11)	(1)	(2)	(3)	(4)
Second week May (16-18)	(2)	(3)	(1)	(4)
Third week May (24-26)	(3)	(1)	(2)	(4)
Fourth week June (6-8)			(4)	(1) (2) (3)
Fifth week*		(4)		(1) (2 (3)
Sixth week*	(4)			(1) (2) (3)

* Planned, but not executed.

All reactions were observed at 24 and 48 hours after injection. Two diameters at right angles were measured and the height estimated. Only average diameters were used since they were considered less subject than single measurements to distortion caused by the animals' position.

RESULTS

The findings are shown in table 2. Each entry is an average of the observations on five animals, except in *Group 4* where the multiple test "readings" represent averages of fifteen measurements (three "readings" for each of five animals).

In spite of repeated weekly multiple tests on this *Group 4*, no progressive

change in the direction of either increased or decreased sensitivity, such as would be expected with either the development of sensitization or desensitization to a protein, was observed.

It will be noted that the time between single and multiple "readings" for each substance varies from group to group. The effect of the different time intervals between the two tests was investigated by a simple analysis of variance. No effect due to this difference was detectable and, therefore, the results with each substance for all three groups were pooled for further analysis.

TABLE 2

AVERAGE SKIN REACTIONS IN GUINEA PIGS TESTED WITH A SINGLE SUBSTANCE OR WITH THREE SUBSTANCES SIMULTANEOUSLY

SUBSTANCE TESTED	GROUP OF GUINEA PIGS	WEEKS DELAY BETWEEN SINGLE AND MULTIPLE TESTS	AVERAGE DIAMETERS (MM.)				HEIGHTS (MM.)			
			24 Hours		48 Hours		24 Hours		48 Hours	
			Single	Multiple	Single	Multiple	Single	Multiple	Single	Multiple
PPD-S	(1)	3	21.9	16.8	18.3	14.0	2.6	2.2	2.4	2.4
	(2)	2	19.0	16.4	17.0	16.1	2.4	2.6	2.0	2.4
	(3)	1	17.9	19.2	17.0	15.9	2.2	2.6	2.4	2.8
	Average		19.6	17.5	17.4	15.3	2.4	2.5	2.3	2.5
A 4	(1)	1	25.7	23.0	23.5	23.5	3.4	3.8	2.8	3.8
	(2)	3	23.5	24.7	23.4	27.9	3.4	4.0	3.4	4.2
	(3)	2	24.0	25.6	23.3	25.5	3.2	4.4	3.2	4.2
	Average		24.4	24.4	23.4	25.6	3.3	4.1	3.1	4.1
C	(1)	2	18.3	16.3	17.8	12.4	2.4	2.0	2.0	2.0
	(2)	1	17.4	14.4	20.4	13.2	2.0	1.8	2.4	1.8
	(3)	3	17.1	16.7	16.7	16.8	2.4	2.2	2.2	2.8
	Average		17.6	15.8	18.3	14.1	2.3	2.0	2.2	2.2
PPD-S	(4)			13.7		12.0		1.8		1.7
A 4	(4)			21.1		19.3		2.9		2.7
C	(4)	−2 Average*	18.5	12.7	15.1	9.7	2.4	1.4	2.8	1.3

* Multiple tests given in each of the first three weeks and single tests in the fourth week.

For the most part, the differences between single and multiple tests are not very striking. These differences are compared with the variations in the differences between individual animals (individual data not shown) by means of the familiar *t*-test (difference/standard deviation of differences (7) (table 3)).

It must be remembered that these averages reflect differences between the two observers as well as differences between single and multiple tests. The testing of *Group 4* with substance C permits a rough comparison between observers, since for *Groups 1*, *2*, and *3* the single tests were examined by the first observer and the multiple tests by the second; while for this group the reverse

was true. The difference between observers is estimated by half the difference between the two means for substance C. If the 24-hour and 48-hour readings are combined, there is a 1.3 mm. average difference in reading diameters and 0.69 mm. average difference in "reading" heights. Thus, it may be that the differences in the first three lines of table 3 are somewhat too small.

The effect of single versus multiple testing on the average diameter of the reactions seems doubtful in the case of PPD-S and A 4. However, in view of the indication of a positive difference between observers, it may be that the larger reactions in single tests with PPD-S should be considered significant.

TABLE 3

AVERAGE DIFFERENCES IN REACTIONS (SINGLE TEST MINUS MULTIPLE TEST) WITH SIGNIFICANCE TESTS

SUBSTANCE	DIFFERENCE IN AVERAGE DIAMETERS						DIFFERENCE IN HEIGHTS					
	24 Hours			48 Hours			24 Hours			48 Hours		
	Average Difference	Standard Deviation of Average Difference	t*	Average Difference	Standard Deviation of Average Difference	t*	Average Difference	Standard Deviation of Average Difference	t*	Average Difference	Standard Deviation of Average Difference	t*
Groups 1, 2 and 3 combined												
PPD-S	2.1	1.2	1.8	2.1	0.9	2.4*	−0.07	0.15	−0.4	−0.27	0.15	−1.7
A 4	−0.03	1.3	−0.02	−2.2	1.7	−1.3	−0.73	0.18	−4.0*	−0.93	0.23	−4.1*
C	1.8	0.7	2.6*	4.2	1.6	2.6*	0.27	0.18	1.5	0.00	0.23	0.0
Group 4												
C	5.8	1.6	3.6*	5.4	1.2	4.7*	1.00	0.38	2.6*	1.53	0.13	11.5

* The chance of t being greater than 2.1 or less than −2.1 is less than one in twenty when the true difference is zero.

Further testing would be required to verify this. The findings in the case of substance C, however, are statistically significant irrespective of the order of the observers and may be viewed as a strong indication of somewhat larger reactions to this substance in single tests.

With respect to the height of reactions, only A 4 appears to be affected. In this case the heights appear to be increased in the multiple tests. Again, in view of the apparent difference between observers, the reality of this effect appears doubtful.

SUMMARY

An experiment was designed to investigate differences in reactions when three different tuberculin protein fractions were given one at a time or several at a time. One was the C protein, less potent, and the other, A 4, more potent, than the standard product, PPD-S.

No evidence was found of a progressive increase or decrease in sensitivity due to repeated tests with any of these substances.

The difference between single and multiple tests with all the substances were on the whole small. However, the reactions to one tuberculin protein fraction (substance C) were significantly smaller when given with other substances than when given alone.

SUMARIO

Efectos de las Cutirreacciones Simultáneas sobre el Tamaño de las Reacciones a la Tuberculina

El experimento descrito se proponía investigar las diferencias en las reacciones cuando se administraban tres diversas fracciones proteínicas de la tuberculina ya por separado o varias a la vez.

No se descubrieron signos de aumento o disminución gradual de la sensibilidad por virtud de pruebas repetidas con ninguna de dichas substancias.

En conjunto, las diferencias entre las reacciones únicas y múltiples con todas dichas substancias fueron pequeñas. Sin embargo, las reacciones a una fracción proteínica de la tuberculina (substancia C) fueron significativamente menores cuando se administraba la misma con otras substancias que cuando se administraba sola.

RESUME

Les effets de tests cutanés simultanés sur l'importance de la réaction à la tuberculine

Une expérience a été faite pour étudier les différences qui se manifestent dans les réactions, quand trois fractions différentes de protéine tuberculinique sont données séparément ou simultanément. Une de ces fractions était la protéine C (moins active) et l'autre la protéine A 4 (plus active) que le produit étalon PPD-S.

La preuve d'une sensibilité progressivement croissante ou décroissante n'a pu être obtenue à la suite de tests répétés avec l'une quelconque de ces substances.

Dans l'ensemble, les différences entre les tests simples et les tests multiples avec toutes ces substances ont été peu marquées. Toutefois, les réactions à la fraction de protéine tuberculinique (substance C) ont été notablement plus faibles quand celle-ci était administrée avec d'autres substances, que lorsqu'elle était employée seule.

Acknowledgment

The helpful assistance of Mildred Meekins is gratefully acknowledged.

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Case Reports

TRANSTHORACIC REMOVAL OF CALCIFIED LYMPH NODE CAUSING HEMOPTYSIS BY BRONCHIAL EROSION[1]

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INTRODUCTION

Calcified peribronchial lymph nodes occasionally erode through the bronchial wall and hemoptysis of varying severity may be caused by such broncholiths. In some instances the sudden coughing up of blood may be the first warning of the lesion. Since a lymph node which ulcerates into the bronchus often causes some narrowing of the lumen, suppuration and bronchiectasis distal to the bronchostenosis is common.

Endoscopic removal of calcified particles from the bronchus has been performed occasionally. When the intrabronchial mass is removed early, irreversible inflammatory changes in the lung distal to the bronchial lesion may be avoided. Often surgical resection of the involved portion of the lung is necessary because suppuration and bronchiectasis have already occurred when the patient comes to definitive treatment. With early antimicrobial treatment of pulmonary inflammations, the development of bronchiectasis may be delayed.

Bronchoscopic removal of a calcified lymph node which is eroding into a bronchus is feasible when the involved bronchus is endoscopically accessible and a sufficient portion of the broncholith projects into the lumen to enable one to grasp the object with an instrument. When surgical intervention is indicated, removal of a part of the lung is usually necessary because the stenosis of the bronchus has caused distal bronchiectasis. Transthoracic removal of a calcified node without sacrifice of any lung tissue may be feasible, however, when the eroded bronchus is endoscopically inaccessible and secondary bronchiectasis has not yet occurred. Such a case is here reported.

CASE REPORT

L. K., a 47-year-old male, complained of an hemoptysis which had occurred without any previous pulmonary symptomatology. A small amount of blood was expectorated for five days. Physical examination was essentially negative except for moderate hypertension. No rales or other abnormal findings were noted on auscultation of the lungs. Roentgenograms of the chest showed no definite pulmonary infiltration, but some areas of calcification were noted in the lower portion of the right hilum. Tomographic studies showed a rather large calcified node adjacent to the right lower lobe bronchus and two small irregular calcific masses near the middle lobe bronchus (figure 1).

Bronchoscopy showed only very slight reddening of the mucosa around the middle lobe orifice but no stenosis or ulceration. There was no blood in the bronchial tree at the time of the endoscopic examination.

Since the clinical, roentgenographic, and bronchoscopic examinations revealed no other explanation for the hemoptysis, it was considered probable that the bleeding was related to the calcified nodes. It was regarded as unlikely that the hypertension was a factor. The situation was discussed frankly with the patient and operative intervention decided upon.

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Operation: On March 24, 1950, a right thoracotomy was performed. The right lung was free of adhesions and appeared normal. In the posterior portion of the hilum, at approximately the level of the superior segment of the lower lobe, a stony hard mass measuring approximately 2 cm. in its greatest diameter was present in a lymph node. This calcified mass was fairly smooth and there was no evidence of abnormal adherence to the bronchial wall, but there was increased vascularity around the lymph node. The two other calcified

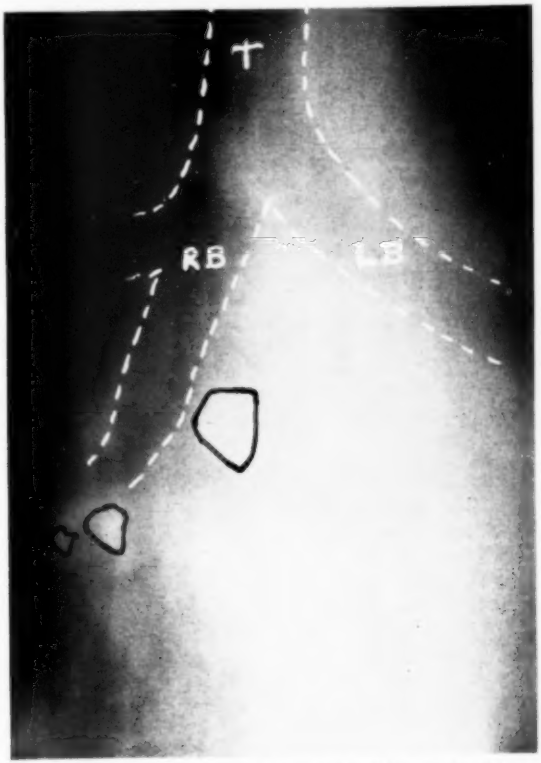

FIG. 1. Retouched tomogram showing the size and location of the three calcified lymph nodes which were visible roentgenographically. The smallest one was the one responsible for the hemoptysis. T—trachea; RB—Right bronchus; LB—Left bronchus.

lymph nodes were difficult to feel and would have been overlooked had it not been for their visualization on the tomograph. They were in close proximity to the middle lobe bronchus just below the branch of the superior pulmonary vein to the middle lobe. Each calcified mass was freed by blunt dissection from its attachment to the adjacent bronchus in order to avoid confusion between bronchial penetration caused by the calcified node and inadvertent injury to the bronchus by sharp dissection. After each calcified mass was removed, the bronchial wall was tested for air leakage by covering it with saline while positive intrabronchial pressure was applied by the anesthetist. The largest calcified mass was first removed.

Then the small calcified masses in the lymph nodes adjacent to the middle lobe bronchus were located and removed. When the third and smallest of these masses was removed, it was seen to have a small sharp projection, and slight air leakage from the bronchus was demonstrated. It was believed that this node had been responsible for the patient's hemoptysis. The minute defect in the bronchus was closed by interrupted fine silk sutures approximating the peribronchial tissue over the opening.

The postoperative course was uneventful. On a re examination fifteen months after operation, the patient denied any pulmonary symptoms and had had no further hemoptysis. Radioscopic examination of the chest showed no abnormality.

DISCUSSION

Many patients with bronchol ithiasis do not have a history of hemoptysis even though a large number of stones may have been coughed up. Schmidt, Clagett, and McDonald (1) noted hemoptysis in 22 per cent of the 41 cases of bronchol ithiasis which they studied. In six of these nine patients, however, hemorrhages of such severity had occurred that transfusion had been required. Their data suggest that if a frank hemoptysis has once occurred there is a considerable chance of further bleeding. The calcareous mass may have sharp edges and penetrate a vessel in a way similar to the behavior of a sharp, hard, foreign body. Hemoptysis is unpredictable in its occurrence and severity. In view of this, it was considered reasonable to remove such a calcified lymph node transthoracically in a case in which the site of penetration was not visible bronchoscopically, although the patient had had only one hemoptysis and had not yet shown any signs of secondary suppuration. As a result of such early therapy, no pulmonary tissue had to be sacrificed and the patient was spared the threat of further hemoptyses.

Transthoracic surgical removal of a calcified lymph node which has caused an hemoptysis by erosion into a bronchus will be a feasible method of treatment only if certain points are carefully observed. Usually a number of calcified nodes are present. The maximum information concerning the number and location of such calcified lymph nodes must be obtained by tomographic films. The relation of the nodes to the bronchial tree must be noted. The region of the eroding calcified node must be carefully determined by roentgenographic studies in various projections taken near the time of the hemoptysis when infiltration may be present due to retained blood or pneumonitis. These roentgenographic findings must be interpreted in conjunction with other data because the retained blood, if present, may have spilled over into some other portion of the bronchial tree and the films alone may give misleading information. Physical findings, such as rales or localized wheeze, may aid in localization. Bronchoscopic examination is important because it may indicate the bronchus from which the blood is coming or reveal other abnormalities such as inflammation of a bronchial orifice. Obviously, the problem is more complex when more than one or two calcified areas are seen on the roentgenogram. The size of a calcified shadow gives no clue to whether it is a bronchol ith. If a careful study fails to establish the site of bleeding with reasonable certainty, it may be best to delay the decision concerning thoracotomy, depending on the severity of the bleeding. Moreover, the occurrence of hemoptysis in a patient with roentgenographically demonstrated hilar calcifications does not necessarily indicate that the two findings are related; not infrequently the bleeding is due to some other cause, notably bronchogenic carcinoma. Considering the great frequency of roentgenographic demonstration of the presence of calcified hilar and mediastinal lymph nodes, bronchial erosion of such nodes is a rare complication.

A calcified lymph node in close anatomic proximity to the esophagus may be associated with a traction diverticulum of the esophagus. Rarely, such a situation may result in an esophagobronchial fistula with severe hemoptysis (2).

SUMMARY

Most broncholiths which require treatment are either removed bronchoscopically or, when irreversible pulmonary suppuration has supervened, by surgical resection of the involved portion of the lung. Occasionally, as in the case reported, hemoptysis may be the presenting symptom of erosion of the bronchus by a calcified lymph node, and insufficient bronchial obstruction to cause pulmonary suppuration may be present. Since the site of bronchial ulceration was not accessible endoscopically, transthoracic surgical removal of the calcified lymph node was performed. The preoperative studies and the points in operative technique which seem important are discussed. Tomography was of great aid in localization of the small calcified mass responsible for the hemoptysis.

SUMARIO

Resección Transtorácica de Ganglio Linfático Calcificado y Ocasionando Hemoptisis por Erosión Bronquial

La mayor parte de los broncolitos que requieren tratamiento son bien extraídos broncoscópicamente o, si ha sobrevenido supuración pulmonar irreversible, por resección quirúrgica de la porción afectada del pulmón. De cuando en cuando, como en el caso ahora comunicado, la hemoptisis puede ser el síntoma evidente de erosión del bronquio por un ganglio linfático calcificado, y puede haber una oclusión bronquial insuficiente para producir supuración pulmonar. Como el asiento de la ulceración bronquial no era accesible endoscópicamente, se ejecutó la extirpación quirúrgica transtorácica del ganglio calcificado. Discútense los estudios preoperatorios y los puntos de la técnica quirúrgica que parecen importantes. La tomografía resultó de mucho valor en la localización de la tumefaccioncita calcificada que ocasionaba la hemoptisis.

RESUME

Ablation transthoracique d'un ganglion lymphatique calcifié déterminant l'hémoptysie par érosion bronchique

La plupart des calcifications bronchiques qui requièrent un traitement sont extraites, soit par bronchoscopie, soit par résection chirurgicale du segment pulmonaire intéressé quand survient une suppuration pulmonaire irréversible. Occasionnellement, comme dans le cas cité, l'hémoptysie peut être le symptôme visible de l'érosion de la bronche par un ganglion lymphatique calcifié et il peut exister une obstruction bronchique insuffisante pour déterminer une suppuration pulmonaire. Comme le siège de l'ulcération bronchique n'était pas accessible par la voie endoscopique, il a été procédé à l'exérèse transthoracique du ganglion lymphatique calcifié. Les études préopératoires et les points de technique opératoire paraissant importants sont discutés. La tomographie a été extrêmement utile pour permettre la localisation de la petite masse calcifiée responsable de l'hémoptysie.

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A RARE COMPLICATION OF TUBERCULOUS MESENTERIC LYMPHADENITIS[1]

A Case of Fatal Hemorrhage from Abdominal Aorta into Jejunum Through a Tuberculous Lymph Node

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(Received for publication September 14, 1951)

The present report is concerned with an unusual complication of tuberculous mesenteric adenitis.

CASE REPORT

The patient, F. S., was a 46-year-old housewife and waitress whose chest roentgenograms revealed changes compatible with minimal pulmonary tuberculosis in April 1946. She was not seen for follow-up observations until after pulmonary symptoms developed late in 1947. At the time of her first admission to Iola Sanatorium in February 1949, she had far advanced tuberculosis with bilateral cavitation. The sputum contained acid-fast bacilli on stained smear.

Clinical examinations: On physical examination, the patient was a fairly well-developed, slender white woman in no acute distress. Temperature was 37.6° C.; pulse was 90 and respirations were 20 per minute; blood pressure was 118 systolic and 80 diastolic in mm. of mercury. Examination of the lungs showed bilateral apical dullness and scattered fine rales throughout the upper two-thirds of the left lung. There was some increase in whispered voice over the right apex posteriorly and many fine rales were noted throughout the upper two-thirds, with some coarse rales posteriorly at the apex. The heart was not enlarged to percussion; occasional extrasystoles were heard on auscultation.

Roentgenographic examination: A chest roentgenogram revealed heavy, diffuse infiltration throughout the upper half of the right lung, with evidence of multiple small cavities throughout this region and slight scattered infiltration throughout the remainder of the lung. On the left there was moderately heavy, diffuse, scattered infiltration throughout the upper two-thirds except at the apex, slight scattered infiltration in the lower third. There was at least one definite small cavity in the infraclavicular region.

Course: The patient gradually improved on bed rest. She decided to leave against advice in order to close up her home. Pneumoperitoneum was started in order to help prevent progression of her pulmonary tuberculosis on such increased activity. Four days after the start of pneumoperitoneum, March 28, 1949, she left the sanatorium, returning to the dispensary for pneumoperitoneum refills at one- to two-week intervals for five months. She then complained of increasing distension, diffuse abdominal pain, and fever. Peritoneal fluid was noted on physical examination and fluoroscopy. Pneumoperitoneum was discontinued, and she was readmitted to the sanatorium on September 21, 1949.

Examination at time of second admission to hospital: At this time the patient was markedly undernourished and appeared chronically and moderately acutely ill. Temperature was 38.3° C.; the pulse was 100; respirations were 24; the blood pressure was 105 systolic and 70 diastolic in mm. of mercury. There were numerous coarse rales over the upper two-thirds of both lung fields, with increased breath sounds and increased whispered voice. A systolic murmur was heard along the left sternal border. The abdomen was distended and shifting dullness was present. The fingers were clubbed.

[1] From Iola Sanatorium, Rochester, New York, and the Surgical Department of the University of Rochester School of Medicine and Dentistry, Rochester, New York.

Chest roentgenograms showed no great change from those of her previous admission. The total leukocyte count was 15,000 per cu. mm. with 84 per cent neutrophils. Urinalysis was normal. Sputum contained acid-fast bacilli on stain of direct smear. Abdominal paracentesis, on September 27, 1949, yielded 1,300 cc. of straw-colored fluid which was sterile on culture for pyogenic organisms and tubercle bacilli. The media used were blood agar plates, brain infusion broth, and a modified Petroff's medium.

Course: The patient received 1 gm. of streptomycin intramuscularly daily from September to November 1949 for a total of 50 gm. By early October, so little abdominal fluid was present that paracentesis was not repeated. She continued to have generalized abdominal distress and anorexia even on a soft diet. There was always abdominal tenderness, and loops of bowel were palpable. Chest roentgenograms showed little change. Temperature ranged from 37.5° to 38.5° C. Sputum consistently contained acid-fast bacilli on stained smears of three-day concentrates. A culture of February 1950 sputum showed the tubercle bacilli to be completely insensitive to streptomycin.

p-Aminosalicylic acid, 10 gm. a day in divided doses, was started on February 22, 1950. Early in March she first complained of fairly constant lower abdominal pain which intermittently radiated through to the back. The impression was that the pain was probably due to the formation of adhesions. On March 3, 1950, the total leukocyte count was 19,000 per cu. mm., with 86 per cent neutrophils; the erythrocyte count was 4.45 million per cu. mm.; the hemoglobin was 12.6 gm. per 100 cc. *p*-Aminosalicylic acid was stopped on March 3, 1950. Periodic urinalyses were essentially negative. Intravenous pyelogram on April 1, 1950, showed only questionable blunting of the calyces on the right. However, the plain film taken before dye injection showed a fairly dense mass measuring approximately 4 by 6 cm. lying to the left of the second and third lumbar vertebrae.

Acute episode: The patient vomited undigested food three times on the morning of April 5, 1950. Later that morning the abdominal pain decreased, but there was marked tenderness in the mid-epigastrium for the first time. That evening, while sitting up to eat supper, she became faint and pulseless. At 5:15 p.m. she was pale, with rapid irregular pulse. She was not cyanotic or dyspneic, was conscious, and complained only of coldness and numbness. Fifteen minutes later, she passed a large tarry stool, after which her blood pressure was 62 systolic and 40 diastolic in mm. of mercury; the pulse was irregular and the heart sounds were of poor quality with many extrasystoles. There were no changes in pulmonary signs. The abdomen was flat and silent except for occasional peristaltic rushes. Physiologic saline was given by vein and the patient's general condition improved slightly, although at six o'clock she passed another tarry stool and vomited a large amount of fluid with the color and consistency of prune juice. The blood pressure was then 84 systolic and 40 diastolic in mm. of mercury. At 7:30 p.m., she passed an enormous "currant jelly" stool and fifteen minutes later she collapsed and blood pressure was unobtainable. She did not respond to stimulants or positive pressure oxygen, and died at 8:02 p.m.

POST-MORTEM EXAMINATION

Macroscopic examination: At autopsy the cause of this massive fatal hemorrhage was not immediately apparent. The abdominal cavity was virtually obliterated by innumerable dense fibrous adhesions which bound all the viscera together firmly. The remaining serosal surfaces of the small intestine were studded with multiple tiny tubercles. A retroperitoneal mass, measuring 4 by 3 cm., to which a loop of jejunum was firmly adherent lay in the region of the ligament of Treitz. On section it contained a cavity lined by laminated clotted blood. The wall varied in thickness. This cavity communicated with the first part of the jejunum through two fistulas, the larger of which was 1½ cm. in diameter. The cavity also communicated with the abdominal aorta approximately 2 cm. above the iliac bifurcation through an elliptical opening measuring 0.8 by 0.4 cm. The opening was through an area where the aortic wall was composed of a firm, raised, yellow plaque (figure 1). Other mesenteric lymph nodes were not enlarged.

Microscopic examination: Histologic examination of tissue from the site of aortic rupture

FIG. 1. Gross specimen showing abdominal aorta with the false aneurysm at site of atheromatous plaque. Probe extends through the rupture in aorta and out into jejunum.

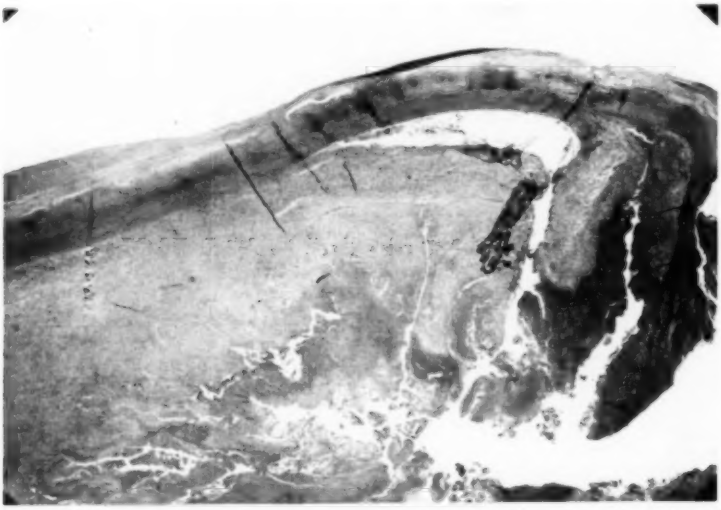

FIG. 2. Histologic specimen showing atherosclerotic abdominal aorta and margin of fistula.

revealed necrotic tuberculous tissue in the adventitia and periaortic lymph nodes. The aortic intimal surface contained lipid and cholesterol deposits characteristic of atherosclerosis. The elastic fibers of the media at the margin of the fistula were frayed out into chronically inflamed and necrotic granulation tissue adjacent to layered thrombus material. There was dense fibrosis in and around the tuberculous adventitia, with a necrotic central zone which formed a small cavity (figure 2).

A section of jejunum revealed an edge of the sinus tract. The jejunal mucosa ended abruptly at this margin and the tuberculous granulation tissue extended through the entire thickness of the intestinal wall. Scattered tubercles were present in the muscularis and serosa, with moderate fibrous thickening of the latter.

The stomach contained approximately 100 cc. of dark-brown fluid; the rugal pattern was intact. The duodenum appeared normal. Both small and large intestines contained a large amount of dark-red fluid and many stringy clots. The mucosal surfaces showed many superficial ulcerations from jejunum to ileum, most numerous in the ileum. The ulcers were round, appeared punched out, with gray bases and measured up to 0.5 cm. in diameter. There was advanced bilateral pulmonary tuberculosis. Tubercles were seen in the liver, spleen, and kidney.

Presumably, a tuberculous mesenteric lymph node had eroded through the adventitial layers of the aorta and caused a false aneurysm at the site of the one area of atherosclerosis; a clot had formed in this false aneurysm. The tuberculous process had also extended from the node into the jejunum bound down over it. Finally, massive bleeding from the aorta through the node into the jejunum had resulted in shock and death.

COMMENT

Tuberculosis of mesenteric lymph nodes associated with tuberculous enteritis is a fairly frequent complication in patients with pulmonary tuberculosis. Mesenteric tuberculosis without demonstrable intestinal lesions is less common but may occur without clinically significant pulmonary lesions. Tuberculous mesenteric lymphadenitis may give rise to varied abdominal complaints which may simulate almost any other acute or chronic intra-abdominal lesion. Numerous cases have been reported in which perforation of caseous mesenteric nodes into the peritoneal cavity has led to generalized peritonitis (1, 2). Also recorded are a few cases in which perforation has been accompanied by erosion of major vessels, with massive intraperitoneal hemorrhage (3, 4, 5, 6).

One case similar to the present one was reported in 1941 by Frosch and Horowitz (7). The patient was a 51-year-old man who had been admitted to the hospital with hematemesis and epigastric pain. Six years earlier he had had epididymectomy and vasectomy for tuberculous epididymitis. In his terminal illness, he responded well at first to a peptic ulcer regimen, but was readmitted with massive hematemesis and died. Post-mortem examination showed no pulmonary tuberculosis. In the lower end of the duodenum there was a perforation, one quarter of an inch in diameter, filled with thrombotic material. From this, a half-inch sinus led into the aorta which had extensive ulcerative athermatous plaques. Cross-section of the area between aorta and duodenum, on histologic examination, revealed a tuberculous lymph node the size of a marble.

In the present case, there are several interesting points in this most unusual set of circumstances. The heavily infected sputum undoubtedly was the cause of the enteric tuberculous ulcerations. It is probable that the retroperitoneal lymph node involvement was a direct extension of this process. The possible role of pneumoperitoneum in the development of tuberculous peritonitis should be considered. It might be postulated that lesions destined otherwise to remain quiescent could be activated by pneumoperitoneum. In view of the present increasing popularity of this procedure, it would be worth while to report

statistics on the incidence of tuberculous peritonitis in patients receiving this form of collapse therapy in various tuberculosis hospitals. Certainly, whether this patient's peritonitis was coincidental or was in some fashion brought on or aggravated by pneumoperitoneum, the firm fibrous adhesions that resulted played a large part in the events that followed. In the normal abdomen with smooth lubricated surfaces between all the viscera, penetration into either the aorta or the jejunum by such an infectious process would be unlikely. Erosion into the free peritoneal cavity would be more apt to occur. Contiguity of the one single area of atheromatous degeneration and the infected lymph node was in this case a fatal coincidence. The type of abdominal pain of which the patient complained during the last month of life could have been produced either by the aortic aneurysm or by the penetrating ulceration of the jejunum.

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Correspondence

To the Editors of The American Review of Tuberculosis:

I cannot help but be disturbed by the leading article in your October 1951 issue (Vol. 64, p. 327) entitled "Tuberculomas of the Mediastinum" by Clifford F. Storey and Harold A. Lyons. At the outset, it is only fair to say that only 5 of their 6 cases described in this article are truly lesions of the mediastinum. One of these 5 had obstructive symptoms referable to the "tumor" and I am sure that no one will question the necessity of operative intervention in this case.

To the trained chest clinician, the chances are that the remaining 4 cases of right upper paratracheal "tuberculoma" in asymptomatic young men with positive tuberculin test could only remotely be called anything but old-fashioned tuberculous nodes in various stages of involution. I am sure that many of us have seen a large number of such mediastinal "tuberculomas" and long follow-up of such survey-discovered lesions would refute the conclusions of the authors that "virtually all of these patients should be subjected to exploratory thoracotomy." Moreover, I am deeply concerned that surgeons less skillful than Drs. Storey and Lyons in exploring such cases and proceeding with the removal of these innocently behaving tuberculous nodes will not be as fortunate as they were to "avoid tearing adjacent vessels and sacrifice important nerves since these tumors have been firmly adherent to vascular organs, nerve tissues and segments of the bronchial tree." Bearing the latter statement of theirs in mind, and despite the wonderful strides made in chest surgery, the risk of leaving such lesions alone with only a good presumptive diagnosis is at present far less than the minimal risk of the operation. Occasional anesthetic and operative deaths following thoracic exploration, if not reported, are not unknown. On the basis of the available knowledge, I do not think we yet have to call in the surgeon to help us with the diagnosis and to alter the prognosis of the very great majority of small, circumscribed, non-symptom-producing uniformly dense lesions in the right paratracheal region of young people whose tuberculin is positive and who are in good health. These involuting tuberculous nodes and the patients who have them should be left alone. The patient should not be annoyed by too many tests or even be hospitalized.

311 South Third Avenue
Mount Vernon, New York

Sincerely,
Louis Schneider

October 10, 1951

To The Editors of The American Review of Tuberculosis:

On behalf of Dr. Lyons and myself, I wish to express my appreciation to the Editors for their courtesy in permitting me this opportunity to reply to the letter of Dr. Louis Schneider concerning our article on "Tuberculomas of the Mediastinum."

We are naturally delighted to learn of the whole-hearted manner in which he concurs with our opinion that a lesion occupying a certain position within the chest and possessing the roentgenographic characteristics which we described is very likely to represent a mediastinal tuberculoma. Objection must be raised, however, to the statement that the masses described by us represent nothing more than "old-fashioned tuberculous nodes in various stages of involution" and particularly to the inference that they can readily be recognized as such on chest roentgenograms. The lesions reported by us bore no real resemblance to ordinary tuberculous nodes which, as we pointed out, are "usually mul-

tiple and commonly bilateral" and differ in other important respects from the granulomatous masses discussed in our article. I must re-emphasize that the masses which we reported appeared in the roentgenograms as *distinct tumors* and that they were so considered by the roentgenologists, chest clinicians, and thoracic surgeons by whom the cases were reviewed preoperatively.

I have now personally seen 8 proved examples of mediastinal tuberculomas. These include the 5 cases surgically excised which were described in our report, a sixth patient upon whom I operated after our manuscript was submitted to the REVIEW, and two lesions which were removed in the clinic with which I was formerly associated. None of these patients was selected for surgery on the basis of the judgment of a single individual. All were considered in conferences which were participated in by chest specialists of national and international reputation. In not one case was the necessity for surgical exploration seriously questioned. This applied to the 3 cases in which the diagnosis of *mediastinal tuberculoma* was given first consideration as well as to the remaining 5 in which other diagnoses were more strongly entertained. We recognized that our diagnoses were merely presumptive ones and that the definitive diagnosis in each case could only be made after histologic study of the lesion. Our primary indication for surgery in each instance was therefore quite a simple one: we were operating for an undiagnosed mediastinal "tumor." To point out that the lesions which we removed were not tumors is, of course, judgment after the fact. It is interesting to note that in not one of the 8 cases tabulated in the report by Sampson *et al.* was tuberculoma the preoperative diagnosis. I think that we must assume that those cases, too, were reviewed prior to surgery by "trained chest clinicians."

We cannot agree that patients with right paratracheal masses of the type described by us should be "left alone," even though the lesion is observed in an apparently healthy individual with a positive tuberculin. Unfortunately, as Dr. E. D. Churchill recently pointed out, the X-ray examination does not tell us precisely what is wrong (New England J. Med., *245:* 339, 1951); neither does a positive tuberculin test nor a state of apparent good health. A positive preoperative diagnosis of mediastinal tumor is so difficult and, despite the most meticulous investigation, can so seldom be made, that many would agree had Dr. Schneider stated that "the patient should not be annoyed by too many tests and the surgeon should proceed forthwith to perform thoracotomy." My former chief, Dr. John Alexander, repeatedly emphasized the frequency with which it is impossible to diagnose a solitary mediastinal tumor accurately prior to operation, and has taught for many years that thoracotomy usually provides the only acceptable answer. We feel that the serious potentialities of such lesions have been so well established that no further confirmation is needed. We do not feel justified in dismissing, after minimal investigation, any patient with a solitary circumscribed tumorlike mediastinal mass merely on "the chance" that it represents an involuting tuberculous node. Our reasons for removing these masses, once the diagnosis has been made with practical certainty by gross examination at the time of thoracotomy, were clearly set forth in our article and need not be reiterated.

It is pertinent to point out, however, that 5 of the 8 patients discussed in Sampson's report, and 3 of the 6 patients whom I have treated surgically, had definite symptoms referable to the mass. We, of course, have no assurance that the remaining 6 of this group of 14 patients would not, in due course of time, have had symptoms as a result of their lesions had they not been excised.

As to the dangers of surgery, one might advise that no surgeon should undertake thoracic exploration unless he has sufficient training, experience, and technical skill to remove successfully the undiagnosed mediastinal mass for which the operation is being

performed. There have been no mortality, minimal morbidity, and no serious complications among the 13 recorded cases, nor in the 3 unreported cases of mediastinal tuberculomas of which I have knowledge, in which the lesion has been excised.

We believe that many physicians interested in diseases of the chest have seen a number of examples of mediastinal tuberculoma. A report of a series of such cases which have been treated conservatively, with suitable roentgenograms and long-term follow-up data, would be of considerable interest and importance. Such a report would, I anticipate, tend to substantiate the opinion of Dr. Lyons and myself that these lesions tend to occur in a "typical" location and to present a "characteristic" appearance. The value of such a report would be appreciably enhanced if the author would include follow-up data on all other patients whom he observed during the same period of time with a similar mass whose lesion subsequently proved to represent something other than a mediastinal tuberculoma. The tragedies which I encounter in my practice as a result of mediastinal masses which have been "watched" overwhelmingly outnumber the occasional surgical and anesthetic accidents which come to my attention. I do not believe my experience in this connection is unique.

Sincerely,
CLIFFORD F. STOREY

24 LYNWOOD DRIVE
VALLEY STREAM, L. I., N. Y.

November 16, 1951

To the Editors of The American Review of Tuberculosis:

I was alarmed to read Dr. Sven Bergqvist's paper in the October 1951 issue of THE AMERICAN REVIEW OF TUBERCULOSIS, in which he describes the use of hyaluronidase to produce an early appearance of the tuberculin reaction in children vaccinated with BCG. This procedure was suggested by an investigation which showed that guinea pigs infected simultaneously with tubercle bacilli and *Staphylococci* lost weight more rapidly, had a shorter survival time, and reacted sooner and more strongly to tuberculin if the *Staphylococci* were active hyaluronidase producers than if they were not.

It seems clear that, whatever effect hyaluronidase had on the guinea pigs, it was not that of raising their resistance to tuberculous infection, and it seems reasonable to assume that all it did was to enhance the development of hypersensitivity with consequent early and strong tuberculin reactions, loss of weight, and shortened survival time. It may be that a similar mechanism accounts for the aggravating effects of certain other infections, most notably influenzal, on the course of tuberculous disease. It is logical then to argue that the school children whom Dr. Bergqvist vaccinated, and to whom he also gave hyaluronidase, suffered an increment of hypersensitivity without gaining any corresponding increase in resistance.

There is now sufficient evidence to prove that hypersensitivity is an unwelcome though frequent companion of resistance, that its effects are wholly destructive, and that a high degree of hypersensitivity is often associated with low resistance. Dr. Bergqvist's paper suggests that physicians who use the BCG vaccine are preoccupied with producing an early and vigorous tuberculin reaction and that they are inclined to forget that a positive tuberculin reaction merely indicates that a person has previously been infected with tubercle bacilli. Because of the previous infection, not because of the positive tuberculin reaction, a varying degree of resistance which is neither proportional to the intensity of the skin reaction nor to the time in which hypersensitivity can be generated, has usually been established.

It is not likely to help the case for using BCG vaccination when a method of vaccination is described which seems to avoid the application to it of what knowledge we have about the pathogenesis of tuberculosis.

DUNGANNON CHEST HOSPITAL
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Yours faithfully,
E. F. JAMES

November 1, 1951

To the Editors of The American Review of Tuberculosis:

Referring to the letter of Dr. E. F. James, I must reply as follows:

The hyaluronidase of the *Staphylococci* intensified, by its spreading effect, the tuberculous infection in the guinea pigs studied. In the same way testicular hyaluronidase hastened and increased the innocuous infection of BCG in the children we studied. This effect was aimed at acceleration and accentuation in the resistance derived from the vaccination. The increased skin allergy revealed by the Mantoux test is interpreted as mirroring the greater immunity obtained.

There is no reason, we feel, in this connection to enter upon a more general discussion of tuberculin hypersensitivity and its implications.

ST. GÖRANS HOSPITAL,
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SVEN BERGQVIST

December 12, 1951

NOTES

COURSE IN THE "MEASUREMENT OF PULMONARY FUNCTION"

A course in the "Measurement of Pulmonary Function," in Boston, March 24 to 28, 1952, is again being sponsored by the American Trudeau Society, the Massachusetts Tuberculosis and Health League, Harvard Medical School, Tufts College Medical School, and Boston University Medical Society. The course is for physicians interested in diseases of the chest who wish to acquaint themselves with the ABCs of methods of analysis of pulmonary and cardiac function. Clinical demonstrations on patients will be presented. Tuition will be $50. Those interested should write to Dr. Edward J. Welch, 1101 Beacon Street, Brookline 46, Massachusetts.

"HISTORY OF THE AMERICAN SANATORIUM ASSOCIATION"

Copies of the "History of the American Sanatorium Association," Historical Series No. 3, are still available from the National Tuberculosis Association. In view of the close association of the Trudeau Society and the American Sanatorium Association, members who have not yet obtained copies might like this history for their libraries. The price is $1.00.

POSTGRADUATE SCHOLARSHIPS

Four scholarships for the annual postgraduate course of the Trudeau School of Tuberculosis at Saranac Lake, New York, are being offered to Pennsylvania physicians by the Pennsylvania Tuberculosis and Health Society. The course will begin on Monday, April 28, 1952 and continue four weeks. In addition to tuberculosis, consideration will also be given to some phases of other chronic chest diseases, including those of occupational origin. The scholarships are in amounts of $375, of which $100 is for the tuition fee to be paid directly to the Trudeau School by the Pennsylvania Tuberculosis and Health Society. Interested physicians should write to the Society at 311 South Juniper Street, Philadelphia 7.

POSITIONS AVAILABLE

Several positions in tuberculosis hospitals for medical superintendents, staff physicians, and residents are now open for qualified physicians. Those interested should write to the Executive Secretary, American Trudeau Society, 1790 Broadway, New York 19, New York.

ANNUAL MEETING—1952

The Annual Meeting of the American Trudeau Society and the National Tuberculosis Association will be held May 26 to 29, 1952, in Boston, at the Statler Hotel. Members are

urged to make hotel reservations early. The preliminary program will appear in the March issue of the BULLETIN of the National Tuberculosis Association.

FELLOWSHIPS OF THE NATIONAL TUBERCULOSIS ASSOCIATION

As a part of its medical research program, the National Tuberculosis Association, through its medical section, the American Trudeau Society, awards each year a small number of undergraduate, graduate, and teaching-resident fellowships to United States citizens who are attending or who are graduates of American schools and plan to continue investigation and teaching in the United States. Graduate and teaching-resident fellowships, as a general rule, are restricted to applicants with the degree of Doctor of Medicine, Doctor of Philosophy, or a Master's degree in science. With regard to undergraduate fellowships, applicants who may be working for an advanced degree must be acceptable as graduate students to the head of the department of the university in which the investigation will be carried out. Further information may be obtained by writing to the Director of Medical Research, American Trudeau Society, c/o The Henry Phipps Institute, Seventh and Lombard Streets, Philadelphia 47, Pennsylvania.

COURSES IN LABORATORY DIAGNOSIS OF TUBERCULOSIS

In cooperation with the Division of Chronic Disease and Tuberculosis, Public Health Service, the Bacteriology Laboratories of the Communicable Disease Center, Chamblee, Georgia, will offer two courses in the laboratory diagnosis of tuberculosis on the following dates:

April 14–25, 1952
November 10–21, 1952

The courses are open to all grades of employed laboratory personnel who are approved by their state health officers. Practical laboratory training in all phases of tuberculosis bacteriology, including preparation of culture media, microscopy, cultural procedures, diagnostic use of animals, and testing of drug sensitivity, will be included in the course. No tuition or laboratory fees are charged. Reservations for the courses should be made well in advance.

In addition, two similar courses will be given for laboratory directors, senior laboratory staff members, physicians, and others of comparable professional standing on the following dates:

May 19–23, 1952
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Additional information and applications may be obtained from the Officer in Charge, Laboratory Training Services, Communicable Disease Center, Public Health Service, P. O. Box 185, Chamblee, Georgia.

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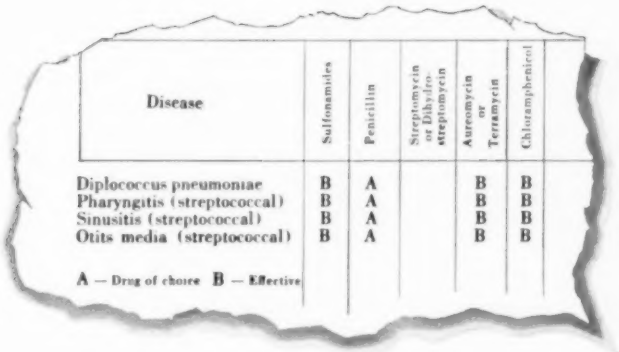

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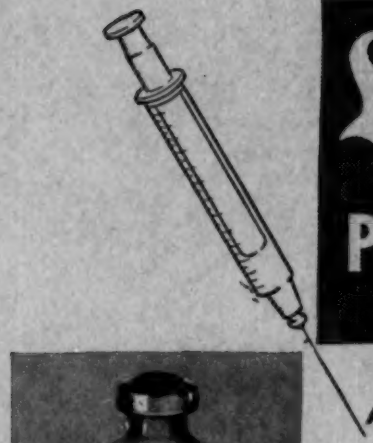

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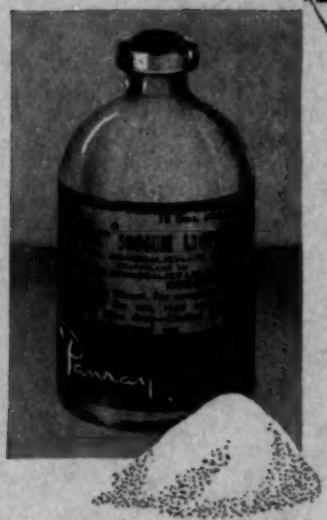

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REFERENCES: 1. "Current Status of Antimicrobial Therapy," Am. Rev. Tuberculosis, 1951, 63, 573. 2.Cutler, J. W., Extrapleural Pneumothorax in Collapse Therapy," J. Thoracic Surg., 1951, 21, 217. 3."Meningeal and Acute Miliary Tuberculosis," Trans. 10th VA Conference Chemotherapy of Tuberculosis, January 1951, pp. 360-369.

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